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NEWS 2 "Ask CAS" for self-help around the clock  
NEWS 3 FEB 25 CA/CAPLUS - Russian Agency for Patents and Trademarks  
(ROSPATENT) added to list of core patent offices covered  
NEWS 4 FEB 28 PATDPAFULL - New display fields provide for legal status  
data from INPADOC  
NEWS 5 FEB 28 BABS - Current-awareness alerts (SDIs) available  
NEWS 6 FEB 28 MEDLINE/LMEDLINE reloaded  
NEWS 7 MAR 02 GBFULL: New full-text patent database on STN  
NEWS 8 MAR 03 REGISTRY/ZREGISTRY - Sequence annotations enhanced  
NEWS 9 MAR 03 MEDLINE file segment of TOXCENTER reloaded  
NEWS 10 MAR 22 KOREAPAT now updated monthly; patent information enhanced  
NEWS 11 MAR 22 Original IDE display format returns to REGISTRY/ZREGISTRY  
NEWS 12 MAR 22 PATDPASPC - New patent database available  
NEWS 13 MAR 22 REGISTRY/ZREGISTRY enhanced with experimental property tags  
NEWS 14 APR 04 EPFULL enhanced with additional patent information and new  
fields  
NEWS 15 APR 04 EMBASE - Database reloaded and enhanced  
NEWS 16 APR 18 New CAS Information Use Policies available online  
NEWS 17 APR 25 Patent searching, including current-awareness alerts (SDIs),  
based on application date in CA/CAPLUS and USPATFULL/USPAT2  
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applications.

NEWS EXPRESS JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT  
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),  
AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005

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=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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=> aplus

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=> file hcaplus

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FULL ESTIMATED COST	0.06	0.27

FILE 'HCAPLUS' ENTERED AT 16:42:37 ON 26 APR 2005

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FILE COVERS 1907 - 26 Apr 2005 VOL 142 ISS 18

FILE LAST UPDATED: 25 Apr 2005 (20050425/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s testosterone

L1 57193 TESTOSTERONE

=> s l1 and prodrug

9747 PRODRUG

L2 48 L1 AND PRODRUG

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=> s 12 and ether  
459975 ETHER  
L3 6 L2 AND ETHER

=> s 12 and ester  
560072 ESTER  
L4 17 L2 AND ESTER

=> d 13 1-6 ibib hitstr abs

L3 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2002:977668 HCAPLUS  
DOCUMENT NUMBER: 138:61309  
TITLE: Enhanced steroidal drug delivery in transdermal  
systems  
INVENTOR(S): Houze, David; Nguyen, Viet  
PATENT ASSIGNEE(S): Noven Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 49 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102390	A1	20021227	WO 2002-US16579	20020618
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1406633	A1	20040414	EP 2002-749537	20020618
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
BR 2002010516	A	20041005	BR 2002-10516	20020618
JP 2005500299	T2	20050106	JP 2003-504976	20020618
US 2003152613	A1	20030814	US 2002-330279	20021230
US 2003152614	A1	20030814	US 2002-330360	20021230
US 2003152615	A1	20030814	US 2002-330361	20021230
US 2003232073	A1	20031218	US 2002-330281	20021230
PRIORITY APPLN. INFO.:			US 2001-298381P	P 20010618
			US 2001-948107	A 20010907
			WO 2002-US16579	W 20020618

AB A composition for transdermal administration resulting from an admixt. includes a therapeutically effective amount of a drug that includes a parent drug and a **prodrug** and a carrier, wherein the parent drug and **prodrug** are individually present in an amount sufficient for a pharmacol. effect. The admixt. include: a therapeutically effective amount of a steroid and a steroid derivative and a carrier for the steroid. The steroid and the corresponding derivative are present in a weight ratio of 10:1 to 1:10 steroid-corresponding steroid derivative In a preferred embodiment ratio is 6:1 to 1:6. In a preferred embodiment, the corresponding steroid

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derivative is a steroidal ester. In another preferred embodiment, the carrier is a polymer that includes a pressure-sensitive adhesive. In another preferred embodiment, the parent drug is an ACE inhibitor such as ramipril and the **prodrug** is an ACE inhibitor **prodrug** such as ramipril Et and/or Me esters. Thus, a transdermal delivery system contained norethindrone 1.2, estradiol 0.9, norethindrone acetate 2.5, VA-64 15.0, GMS-737 (acrylic PSA), oleic acid 3.0, dipropylene glycol 9.0, and Bio-PSA-7-4603 63.4%.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:435015 HCAPLUS

DOCUMENT NUMBER: 135:33380

TITLE: Benzyl tetralins, formulations and uses thereof as inhibitors of 17 $\beta$ -hydroxy steroid dehydrogenase for treatment of androgen- and estrogen-mediated diseases

INVENTOR(S): Smith, Harold John; Mason, Peter; Ahmadi, Masoud; Nicholls, Paul Joseph; Greer, Valerie

PATENT ASSIGNEE(S): University College Cardiff Consultants Limited, UK

SOURCE: PCT Int. Appl., 44 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

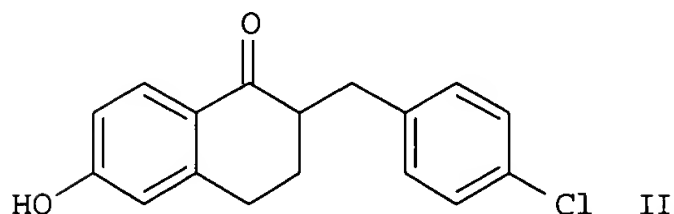
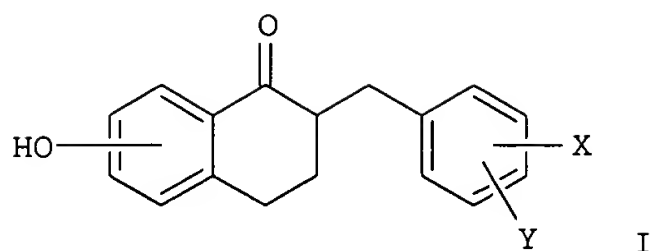
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042181	A1	20010614	WO 2000-GB4700	20001208
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: GB 1999-29302 A 19991210

OTHER SOURCE(S): MARPAT 135:33380

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AB A benzyl tetralin I or a pharmaceutically acceptable salt or **prodrug** thereof is disclosed [wherein X = halogen, C1-6 alkyl (optionally substituted by at least one halogen), a fused bicyclic hydrophobic ring system, or Ph (optionally substituted by at least one halogen); Y = H or halogen; or X and Y together form the residue of a carbocyclic ring]. I are useful as inhibitors of 17 $\beta$ -hydroxy steroid dehydrogenase (17 $\beta$ -HSD) isoforms operable in the steroidogenesis pathway, and have therapeutic applications in the treatment of androgen- or estrogen-dependent or mediated diseases. In particular, I are useful for treating prostate cancer or breast cancer. I may be formulated with other steroidogenesis pathway enzyme inhibitors, where the inhibited enzyme is a 17 $\beta$ -HSD isoform, 5 $\alpha$ -steroid reductase, aromatase P450arom, or estrogen sulfatase. Eight specific examples and their intermediates are described. For instance, 6-methoxy-3,4-dihydronaphthalen-1(2H)-one underwent a sequence of O-demethylation (57%), O-protection as the THP **ether** (86.8%), condensation with 4-chlorobenzaldehyde to give a 2-benzylidene derivative (51.7%), deprotection (94%), and hydrogenation of the benzylidene bond (69.5%), to give title compound II. This compound at 200  $\mu$ M gave 97.9% inhibition of androstenedione reduction by human testicular microsomal 17 $\beta$ -HSD in vitro, and 59.6% inhibition of estrone reduction by human placental cytosolic 17 $\beta$ -HSD in vitro.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1997:557633 HCAPLUS  
 DOCUMENT NUMBER: 127:239118  
 TITLE: Drug delivery systems containing ester sunscreens and penetration enhancers  
 INVENTOR(S): Reed, Barry Leonard; Morgan, Timothy Matthias; Finnin, Barrie Charles  
 PATENT ASSIGNEE(S): Monash University, Australia; Reed, Barry Leonard; Morgan, Timothy Matthias; Finnin, Barrie Charles  
 SOURCE: PCT Int. Appl., 70 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 6  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729735	A1	19970821	WO 1997-AU91	19970219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2244089	AA	19970821	CA 1997-2244089	19970219
AU 9717134	A1	19970902	AU 1997-17134	19970219
AU 706967	B2	19990701		
EP 901368	A1	19990317	EP 1997-904304	19970219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000504697	T2	20000418	JP 1997-528834	19970219
US 6299900	B1	20011009	US 1998-125436	19981218
AU 9952589	A1	19991202	AU 1999-52589	19991001
US 2002028235	A1	20020307	US 2001-910780	20010724
US 6818226	B2	20041116		
US 2004013620	A1	20040122	US 2003-428016	20030502
US 2004013621	A1	20040122	US 2003-428019	20030502
US 2004028625	A1	20040212	US 2003-428012	20030502
US 2004028725	A1	20040212	US 2003-428018	20030502
US 2004096405	A1	20040520	US 2003-636976	20030808
US 2004081684	A1	20040429	US 2003-644085	20030820
US 2004146469	A1	20040729	US 2004-759303	20040120
PRIORITY APPLN. INFO.:			AU 1996-8144	A 19960219
			AU 1997-17134	A3 19970219
			WO 1997-AU91	W 19970219
			US 1998-125436	A3 19981218
			US 2001-910780	A2 20010724
OTHER SOURCE(S): MARPAT 127:239118				
AB	A transdermal drug delivery system which comprises at least one physiol. active agent or <b>prodrug</b> thereof and at least one dermal penetration enhancer; characterized in that the dermal penetration enhancer is a safe skin-tolerant ester sunscreen. A non-occlusive, percutaneous or transdermal drug delivery system which comprises: (1) an effective amount of at least one physiol. active agent or <b>prodrug</b> thereof; (2) at least one non-volatile dermal penetration enhancer; and (3) at least one volatile liquid; characterized in that the dermal penetration enhancer is adapted to transport the physiol. active agent across a dermal surface or mucosal membrane of an animal, including a human, when the volatile liquid evaps., to form a reservoir or depot of a mixture comprising the penetration enhancer and the physiol. active agent or <b>prodrug</b> within said surface or membrane; and the dermal penetration enhancer is of low toxicity to, and is tolerated by, the dermal surface or mucosal membrane of the animal. The mean flux of 2% ketoprofen in 70% volume/volume aqueous ethanol through shed snakes kinetics in presence of 2% octyl salicylate in 70% volume/volume aqueous ethanol was 27.66			
as	compared to 2.58 µg/cm <sup>2</sup> .h for azone. A transdermal aerosol contained 17β-estradiol 2, octyl dimethyl-p-aminobenzoate 8, ethanol 69, and di-Me <b>ether</b> 30%.			
L3	ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN			

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ACCESSION NUMBER: 1996:181570 HCAPLUS  
DOCUMENT NUMBER: 124:233011  
TITLE: Preparation of glycoside prodrugs with enhanced water solubility.  
INVENTOR(S): Klemke, R.-Erich; Koreeda, Masato; Houston, Todd A.; Shull, Brian K.; Tuinman, Roeland J.  
PATENT ASSIGNEE(S): Harrier, Inc., USA  
SOURCE: PCT Int. Appl., 51 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 4  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9532981	A1	19951207	WO 1995-US7027	19950601
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5693767	A	19971202	US 1994-251869	19940601
AU 9526617	A1	19951221	AU 1995-26617	19950601
PRIORITY APPLN. INFO.:				
			US 1994-251869	A 19940601
			US 1991-644002	A2 19910122
			US 1991-733915	B2 19910722
			US 1992-815691	B2 19920124
			US 1993-6447	B2 19930121
			WO 1995-US7027	W 19950601

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\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Glycosides of aliphatic, alicyclic, aliphatic-aromatic, and aromatic aglycons having primary, secondary, or tertiary OH, SH, or CO<sub>2</sub>H groups with 2,3-dideoxy- $\alpha$ -D-erythrohex-2-enopyranoside fragments Q1-Q6 (A = acyl; X = O, S, CO<sub>2</sub>), were prepared. Thus, a mixture of 4-acetamidophenol and hexaacetyl D-maltal was refluxed with iodine in THF for 12 h to give 30% of an  $\alpha,\beta$ -glycoside, which was stirred with Ba(OH)<sub>2</sub> in MeOH to give glycoside (I). I had 8 times the H<sub>2</sub>O solubility of tylenol itself in phosphate-buffered saline at pH 7.4.

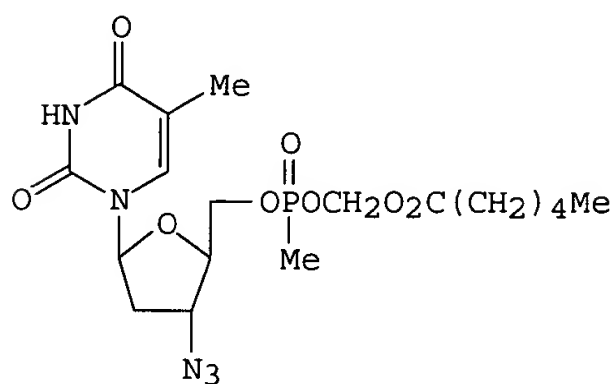
L3 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1992:449157 HCAPLUS  
DOCUMENT NUMBER: 117:49157  
TITLE: Preparation of brain-targeted acyloxymethylphosphonate prodrugs  
INVENTOR(S): Bodor, Nicholas S.  
PATENT ASSIGNEE(S): USA  
SOURCE: PCT Int. Appl., 179 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English

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FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9200988	A1	19920123	WO 1991-US4824	19910712
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
US 5177064	A	19930105	US 1990-553548	19900713
CA 2087194	AA	19920114	CA 1991-2087194	19910712
AU 9183000	A1	19920204	AU 1991-83000	19910712
AU 649466	B2	19940526		
EP 539493	A1	19930505	EP 1991-913701	19910712
EP 539493	B1	19970326		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05509313	T2	19931222	JP 1991-513064	19910712
AT 150759	E	19970415	AT 1991-913701	19910712
US 5413996	A	19950509	US 1992-962504	19921016
US 5618803	A	19970408	US 1994-340896	19941115
PRIORITY APPLN. INFO.:			US 1990-553548	A 19900713
			WO 1991-US4824	A 19910712
			US 1992-962504	A3 19921016
OTHER SOURCE(S):		MARPAT 117:49157		
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AB QP(O)(R1)OCHR2O2CR3 [Q = O-bonded drug moiety; R1 = alkyl, aryl, aralkyl; R2 = H, heteroaryl, (cyclo)alkyl, heterocyclyl, aralkyl; R3 = alkyl, alkenyl, (alkyl)cycloalkyl(alkyl), aryloxyalkyl, pyridyl, (substituted) Ph, phenylalkyl], were prepared. Thus, zidovudine was stirred with MeP(O)Cl2 and Na2CO3 in acetone for 17 h; H2O was added to give 31.3% zidovudine methylphosphonate (I), which was treated with iodomethyl hexanoate and CsF in DMF to give title compound II. Title compds. are rapidly hydrolyzed in vivo, and I was found in the brain after administration of II.

L3 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1990:7383 HCAPLUS  
DOCUMENT NUMBER: 112:7383  
TITLE: Preparation of dihydropyridine-containing prodrugs for brain-specific drug delivery  
INVENTOR(S): Bodor, Nicholas S.  
PATENT ASSIGNEE(S): University of Florida, USA

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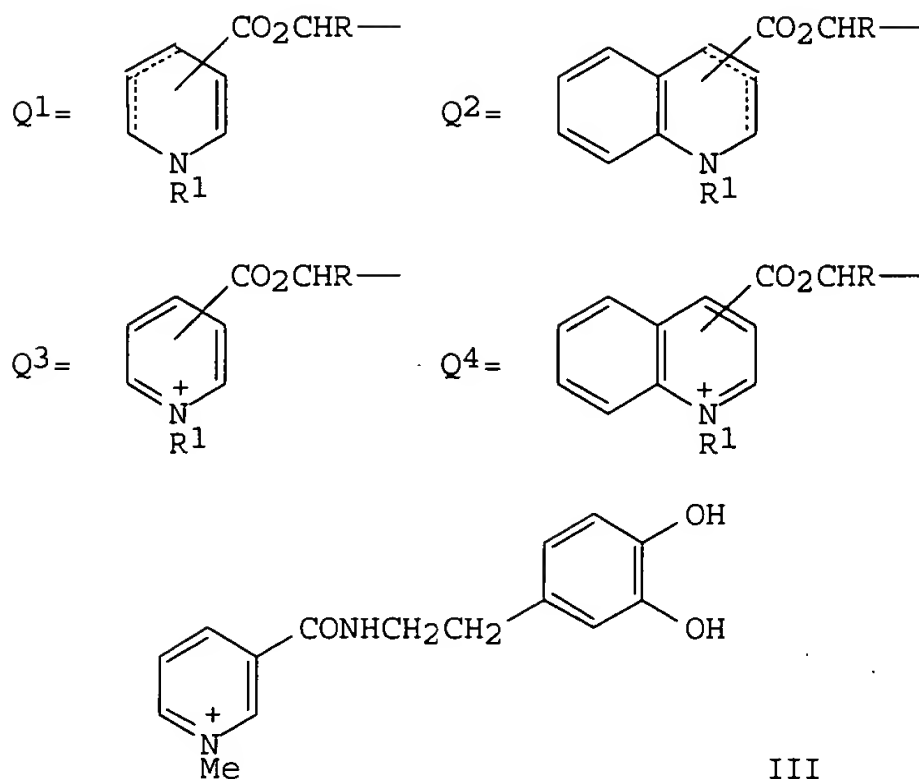
SOURCE: U.S., 282 pp. Cont.-in-part of U.S. 4,479,932.  
 CODEN: USXXAM  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 7  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4824850	A	19890425	US 1984-665940	19841029
US 4479932	A	19841030	US 1982-379316	19820518
US 4622218	A	19861111	US 1983-475493	19830315
EP 218300	A2	19870415	EP 1986-201710	19830512
EP 218300	A3	19880928		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 221588	A2	19870513	EP 1986-201711	19830512
EP 221588	A3	19880921		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 222425	A2	19870520	EP 1986-201714	19830512
EP 222425	A3	19880921		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 224283	A2	19870603	EP 1986-201713	19830512
EP 224283	A3	19880921		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 256577	A2	19880224	EP 1987-201385	19830512
EP 256577	A3	19880706		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 262696	A2	19880406	EP 1987-201384	19830512
EP 262696	A3	19880720		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
CA 1253856	A1	19890509	CA 1983-428192	19830516
ZA 8303521	A	19841224	ZA 1983-3521	19830517
US 4540564	A	19850910	US 1983-516382	19830722
US 4727079	A	19880223	US 1985-733463	19850513
US 4880921	A	19891114	US 1987-75830	19870720
US 4900837	A	19900213	US 1987-76191	19870721
EP 334853	A1	19891004	EP 1987-907186	19871013
EP 334853	B1	19930609		
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AT 90355	E	19930615	AT 1987-907186	19871013
US 4880816	A	19891114	US 1987-116583	19871104
US 5008257	A	19910416	US 1989-295938	19890111
US 5187158	A	19930216	US 1991-639283	19910110
US 5525727	A	19960611	US 1992-967979	19921028
PRIORITY APPLN. INFO.:			US 1982-379316	A2 19820518
			US 1983-461543	A2 19830127
			US 1983-475493	A2 19830315
			CA 1983-428192	A 19830516
			US 1983-516382	A2 19830722
			JP 1982-101940	A 19820614
			EP 1983-902034	P 19830512
			WO 1983-US725	A 19830512
			WO 1983-WO725	A 19830512
			ES 1983-522489	A 19830517
			IE 1983-1149	A 19830517
			ZA 1983-3521	A 19830517
			IT 1983-48327	A 19830518
			US 1984-665940	A2 19841029
			US 1985-733463	A3 19850513

EP 1987-907186	A 19871013
WO 1987-US2590	A 19871013
US 1989-295938	A3 19890111
US 1991-639283	A3 19910110

OTHER SOURCE(S) :  
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CASREACT 112:7383; MARPAT 112:7383



AB Compds. of the formula D(DHC)n (I) [D = residue of a centrally acting drug having anticonvulsant, sedative and/or hypnotic properties, said drug being a hydantoin or barbiturate or an analog of a hydantoin or barbiturate, said drug containing at least one reactive amide or imide functional group, said residue being characterized by the absence of a H atom from at least one of said amide or imide functional groups in said drug; n = pos. integer equal to the number of said functional groups from which a H atom is absent; DHC = reduced, biooxidizable, blood-brain barrier penetrating, lipoidal form of a dihydropyridine-pyridinium salt redox carrier; DHC = Q1, Q2, etc.; R = H, C1-7 alkyl, C3-8 cycloalkyl, C1-7 haloalkyl, etc.; R1 = C1-7 alkyl, haloalkyl, C7-10 aralkyl; dotted line indicates the presence of a double bond in position 4 or 5 of the dihydropyridine ring or position 2 or 3 of the dihydroquinoline ring] were prepared as brain-specific prodrugs. Quaternary salts of the formula D(QC+)nqX-t (II) (D = as given above; X- = anion of a pharmaceutically acceptable organic or inorg. acid; t = valence of acid anion; q = number which when multiplied by t is equal to n; QC+ = hydrophilic, ionic pyridinium salt form of a dihydropyridine-pyridinium salt redox carrier; QC+ = Q3, Q4, etc.; R, R1 = as given above; n = pos. integer equal to the number of said functional groups from which a H atom is absent) were prepared as intermediates for I. Reaction of 5,5-diphenyl-3-hydroxymethyl-2,4-imidazolidinedione with nicotinic anhydride, followed by methylation with MeI and reduction, gave 5,5-diphenyl-3-[(1'-methyl-1',4'-dihydropyridin-3'-yl)carbonyloxymethyl]-2,4-imidazolidinedione. After one single injection of 1-methyl-3-[[N-[β-(3,4-dipivaloxyphenyl)ethyl]]carbamoyl-1,4-dihydropyridine to a rat, the pyridinium compound III could be seen to appear and then to disappear quickly from the blood, with a half-life of

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27 min. On the contrary, the concentration of III increases in the brain steadily, reaching a maximum at about 30 min following administration. For III, the half-life of disappearance from the brain is about 3.2 h.

=> d his

(FILE 'HOME' ENTERED AT 16:42:20 ON 26 APR 2005)

FILE 'STNGUIDE' ENTERED AT 16:42:25 ON 26 APR 2005

FILE 'HCAPLUS' ENTERED AT 16:42:37 ON 26 APR 2005

L1 57193 S TESTOSTERONE  
L2 48 S L1 AND PRODRUG  
L3 6 S L2 AND ETHER  
L4 17 S L2 AND ESTER

=> d l2 1-20 ibib hitstr abs

L2 ANSWER 1 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2005:283298 HCAPLUS  
TITLE: Combinations of chlorpromazine compounds and  
antiproliferative drugs for the treatment of neoplasms  
INVENTOR(S): Lee, Margaret S.; Nichols, James M.; Zhang, Yanzhen;  
Keith, Curtis  
PATENT ASSIGNEE(S): Combinatorx, Incorporated, USA  
SOURCE: PCT Int. Appl., 65 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005027842	A2	20050331	WO 2004-US30368	20040916
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2003-504310P P 20030918  
AB The invention discloses a method for treating a patient having a cancer or other neoplasm by administering chlorpromazine or a chlorpromazine analog and an antiproliferative agent simultaneously or within 14 days of each other in amts. sufficient to treat the patient.

L2 ANSWER 2 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2005:52993 HCAPLUS  
DOCUMENT NUMBER: 142:190557  
TITLE: Antitumor activity of methoxymorpholinyl doxorubicin:  
Potentiation by cytochrome P450 3A metabolism  
AUTHOR(S): Lu, Hong; Waxman, David J.

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CORPORATE SOURCE: Division of Cell and Molecular Biology, Department of  
Biology, Boston University, Boston, MA, USA  
SOURCE: Molecular Pharmacology (2005), 67(1), 212-219  
CODEN: MOPMA3; ISSN: 0026-895X  
PUBLISHER: American Society for Pharmacology and Experimental  
Therapeutics  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Methoxymorpholinyl doxorubicin (MMDX) is a novel liver cytochrome P 450 (P 450)-activated anticancer **prodrug** whose toxicity toward cultured tumor cells can be potentiated up to 100-fold by incubation with liver microsomes and NADPH. In the present study, a panel of human liver microsomes activated MMDX with potentiation ratios directly correlated to the CYP3A-dependent **testosterone** 6 $\beta$ -hydroxylase activity of each liver sample. Microsome-activated MMDX exhibited nanomolar IC50 values in growth-inhibition assays of human tumor cell lines representing multiple tissues of origin: lung (A549 cells), brain (U251 cells), colon (LS180 cells), and breast (MCF-7 cells). Anal. of individual cDNA-expressed CYP3A enzymes revealed that rat CYP3A1 and human CYP3A4 activated MMDX more efficiently than rat CYP3A2 and that human P450s 3A5 and 3A7 displayed little or no activity. MMDX cytotoxicity was substantially increased in Chinese hamster ovary cells after stable expression of CYP3A4 in combination with P 450 reductase. CYP3A activation of MMDX abolished the parent drug's residual cross-resistance in a doxorubicin-resistant MCF-7 cell line that overexpresses P-glycoprotein. CYP3A-activated MMDX displayed a comparatively high intrinsic stability, with a t<sub>1/2</sub> of .apprx.5.5 h at 37°. MMDX was rapidly activated by CYP3A at low (.apprx.1-5 nM) **prodrug** concns., with 100% tumor cell kill obtained after as short as a 2-h exposure to the activated metabolite. These findings demonstrate that MMDX can be activated by CYP3A metabolism to a potent, long-lived, and cell-permeable cytotoxic metabolite and suggest that this anthracycline **prodrug** may be used in combination with CYP3A4 in a P 450 **prodrug** activation-based gene therapy for cancer treatment.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:934160 HCAPLUS

DOCUMENT NUMBER: 141:388650

TITLE: Anti-CD74 immunoconjugates and their therapeutic and diagnostic uses

INVENTOR(S): Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.; Lundberg, Bo B.

PATENT ASSIGNEE(S): Immunomedics, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 44 pp., Cont.-in-part of U.S. Ser. No. 377,122.  
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 7

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004219203	A1	20041104	US 2003-706852	20031112
US 6306393	B1	20011023	US 1999-307816	19990510
US 2002071807	A1	20020613	US 2001-965796	20011001
US 2003124058	A1	20030703	US 2002-314330	20021209

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US 2003133930 A1 20030717 US 2003-350096 20030124  
US 2004115193 A1 20040617 US 2003-377122 20030303  
WO 2004110390 A2 20041223 WO 2004-US19238 20040617

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,  
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,  
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,  
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,  
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,  
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,  
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,  
SN, TD, TG

PRIORITY APPLN. INFO.:

US 1999-307816 A1 19990510  
US 2000-590284 A1 20000609  
US 2001-965796 A1 20011001  
US 2002-360259P P 20020301  
US 2002-314330 A2 20021209  
US 2003-350096 A2 20030124  
US 2003-377122 A2 20030303  
US 2003-478830P P 20030617  
US 1997-41506P P 19970324  
US 1998-38995 A2 19980312  
US 1999-138284P P 19990609  
US 2003-706852 A 20031112

AB Disclosed are compns. that include anti-CD74 immunoconjugates and a therapeutic and/or diagnostic agent. Also disclosed are methods for preparing the immunoconjugates and using the immunoconjugates in diagnostic and therapeutic procedures. The compns. may be part of a kit for administering the anti-CD74 immunoconjugates compns. in therapeutic and/or diagnostic methods. Anti-CD74 binding mols. are conjugated to the one or more lipids by one or more of a sulfide linkage, a hydrazone linkage, a hydrazine linkage, an ester linkage, an amido linkage, an amino linkage, an imino linkage, a thiosemicarbazone linkage, a semicarbazone linkage, an oxime linkage, a carbon-carbon linkage. Anti-CD74 immunoconjugates comprise a drug, a **prodrug**, a toxin, an enzyme, a radioisotope, an immunomodulator, a cytokine, a hormone, an antibody., an oligonucleotide, or a photodynamic agent.

L2 ANSWER 4 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:817876 HCAPLUS

DOCUMENT NUMBER: 141:314155

TITLE: Preparation of xanthenone and acridinone DNA-PK inhibitors as cancer treatment potentiators

INVENTOR(S): Halbrook, James W.; Kesicki, Edward A.; Burgess, Laurence Edward; Schlachter, Stephen T.; Eary, Charles T.; Schiro, Justin G.

PATENT ASSIGNEE(S): Icos Corporation, USA

SOURCE: PCT Int. Appl., 149 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2004085418	A2	20041007	WO 2004-US8459	20040319

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WO 2004085418

A3

20050127

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW  
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

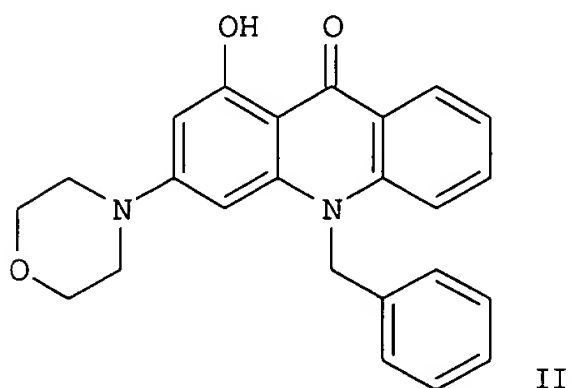
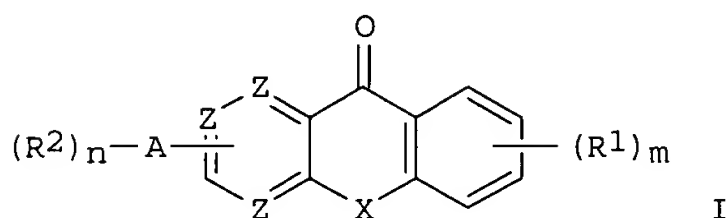
US 2003-456999P

P 20030324

OTHER SOURCE(S):

MARPAT 141:314155

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AB Title compds. I [wherein m = 0-3; n = 0-4; X = O, SOO-2, NRa; Z = independently CRb, N; A = heteroaryl; R1 = independently halo (un)substituted (cyclo)alkyl, heterocyclalkyl, amino carboxy, phosphoryl, acyl, (hetero)aryl, etc.; R2 = independently halo, CHO, (un)substituted alkyl, (hetero)aryl, carbamoyl, carboxy, etc.; R1 = H, (cyclo)alkyl, (hetero)aryl, carboxy, carbamoyl, etc.; Rb = independently H, alkyl, halo, CHO, alkoxy, phosphoryl, amino, carboxy, etc.; and pharmaceutically acceptable salts and prodrugs thereof] were prepared as DNA-dependent protein kinase (DNA-PK) inhibitors. I and their pharmaceutical compns. potentiate cancer treatment by sensitizing cells to an agent that induces DNA lesions. For example, condensation of 1,3-dihydroxy-10H-acridin-9-one with trifluoromethanesulfonic anhydride gave the triflate. Pd-catalyzed substitution of the monoester with morpholine, followed by benzylation provided II. The latter inhibited DNA-PK induced phosphorylation of a p53 peptide substrate with a IC50 of 20 nM.

L2 ANSWER 5 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:606359 HCAPLUS

DOCUMENT NUMBER: 141:134689

TITLE: Method of achieving accelerated fat loss by

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administration of 7-oxo-DHEA or a **prodrug** to  
a dieting mammal  
INVENTOR(S): Zenk, John L.  
PATENT ASSIGNEE(S): Humanetics Corporation, USA  
SOURCE: PCT Int. Appl., 6 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004062606	A2	20040729	WO 2004-US541	20040112
WO 2004062606	A3	20041125		
W:	AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ			

PRIORITY APPLN. INFO.: US 2003-439816P P 20030113  
AB Accelerating fat loss by administering to a dieting mammal the fat loss accelerating agent 7-oxo-DHEA or a pro-drug thereof incapable of in vivo conversion to **testosterone**.

L2 ANSWER 6 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2004:569865 HCAPLUS  
DOCUMENT NUMBER: 141:82949  
TITLE: Method of modulating the basal metabolic rate of a dieting mammal by administration of a metabolic modulating agent to the dieting mammal  
INVENTOR(S): Zenk, John  
PATENT ASSIGNEE(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 3 pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004138303	A1	20040715	US 2003-340980	20030113
JP 2004217657	A2	20040805	JP 2004-4160	20040109
EP 1437138	A1	20040714	EP 2004-543	20040113
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			

PRIORITY APPLN. INFO.: US 2003-340980 A 20030113  
AB Modulating the metabolism of a dieting mammal by administering to the dieting mammal the metabolic modulating agent 7-oxo DHEA or a pro-drug thereof incapable of in vivo conversion to **testosterone**.

L2 ANSWER 7 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2004:355044 HCAPLUS  
DOCUMENT NUMBER: 140:350597  
TITLE: Treating androgen decline in aging male  
(ADAM)-associated conditions with selective androgen

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receptor modulators (SARMS)  
INVENTOR(S): Dalton, James T.; Miller, Duane D.; Steiner, Mitchell  
S.; Veverka, Karen A.  
PATENT ASSIGNEE(S): GTX, Inc., USA  
SOURCE: PCT Int. Appl., 111 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035739	A2	20040429	WO 2003-US32513	20031014
WO 2004035739	A3	20040930		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2005080054	A1	20050414	US 2003-683161	20031014
PRIORITY APPLN. INFO.:			US 2002-418336P	P 20021016

OTHER SOURCE(S): MARPAT 140:350597

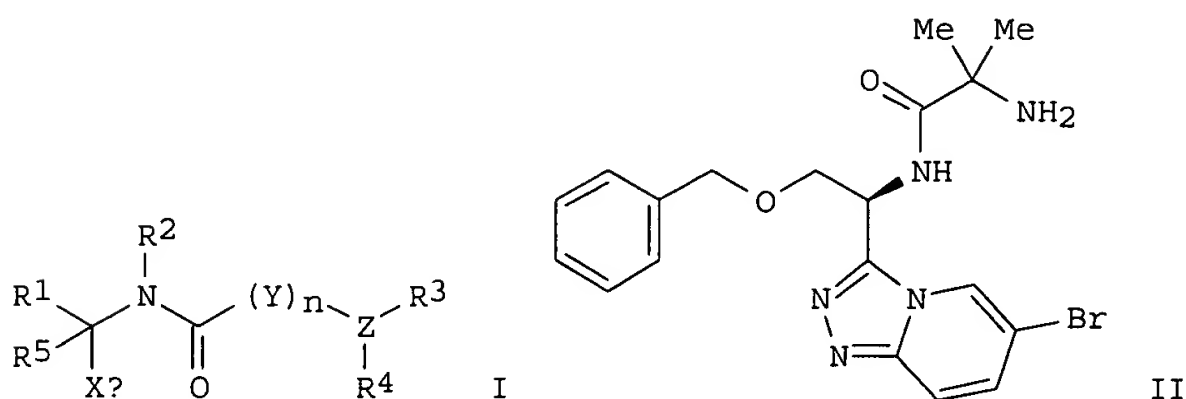
AB The invention provides a method for treating, preventing, suppressing, inhibiting or reducing the incidence of an androgen decline in aging male (ADAM)-associated condition in a male subject, by administering to the subject a selective androgen receptor modulator (SARM) compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, **prodrug**, polymorph, crystal, or any combination thereof. The invention further provides a method of treating, preventing, suppressing, inhibiting or reducing the incidence of sexual dysfunction, decreased sexual libido, erectile dysfunction, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, benign prostate hyperplasia or prostate cancer due to ADAM in a male subject, by administering to the subject a SARM compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, **prodrug**, polymorph, crystal, or any combination thereof.

L2 ANSWER 8 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2004:220151 HCAPLUS  
DOCUMENT NUMBER: 140:270858  
TITLE: Preparation of heterocyclic aromatic compounds useful as growth hormone secretagogues  
INVENTOR(S): Yu, Guixue; Li, Jun; Ewing, William R.; Sulsky, Richard B.; Li, James J.; Tino, Joseph A.  
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA  
SOURCE: PCT Int. Appl., 193 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004021984	A2	20040318	WO 2003-US27513	20030902
WO 2004021984	A3	20041125		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004147568	A1	20040729	US 2003-653410	20030902
PRIORITY APPLN. INFO.:			US 2002-408099P	P 20020904
			US 2003-491645P	P 20030731
OTHER SOURCE(S):		MARPAT 140:270858		
GI				



AB Title compds. I [R1 = (un)substituted alkyl, aryl, alkenyl, alkynyl, etc.; R2, R3 and R4 independently = H, (un)substituted alkyl, aryl, alkenyl, arylalkyl, heterocycle, etc.; or R3 and R4 together form a 3-8 membered cycloalkyl or heterocyclic ring; or one or more of R3 and R4 together with one or more of Y and Z form a mono or bicyclic cycloalkyl or heterocyclic ring; R5 = H, (un)substituted alkyl, cycloalkyl, heterocycle, aryl and heteroaryl; Y = linking group consisting of (un)substituted alkylene, alkenylene, alkynylene, arylene, and heteroarylene; n = integer from 1-6; Z = N; Xa = 2 to 4 fused or spiro cycloalkyl, heterocycle, aryl or heteroaryl rings wherein one or more of said rings may be optionally substituted with 1-5 substituents of Ra or Rb; Ra and Rb independently = CN, CO, halo, alkyl, alkenyl, alkynyl, arylalkyl, etc.] and their methods of preparation are provided that are useful in stimulating endogenous production or release of growth hormone (no data). Thus, e.g., II·HCl was prepared via amidation of 3-benzyloxy-2-tert-butoxycarbonylamino propionic acid with 5-bromopyridin-2-yl hydrazine and subsequent cyclocondensation with trimethylsilyl azide, deprotection, amidation with 2-tert-butoxycarbonylamino-2-methylpropionic acid, deprotection and conversion to HCl derivative with acid washing. The compds. provided herein are claimed as useful in treating obesity, osteoporosis (improving bone d.) and in improving muscle mass and muscle strength.

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L2 ANSWER 9 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:836591 HCAPLUS  
DOCUMENT NUMBER: 139:333131  
TITLE: Methods for improving efficacy of treatment with  
growth hormone secretagogues  
INVENTOR(S): Fryburg, David A.; Taylor, Ann E.  
PATENT ASSIGNEE(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 25 pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003199514	A1	20031023	US 2003-392527	20030320
PRIORITY APPLN. INFO.:			US 2002-368455P	P 20020327
OTHER SOURCE(S):	MARPAT 139:333131			

AB The present invention provides methods of increasing efficacy of treatment with growth hormone secretagogues, prodrugs thereof and pharmaceutically acceptable salts of said secretagogues and said prodrugs, for patients who have normal or above normal levels of **testosterone**. The present invention also provides methods of reducing the therapeutic doses of such compds. in such patients. More specifically, the present invention provides such methods wherein the growth hormone secretagogues are (I: HETCOC(R3)(R4)N(X4)COR6N(R7)R8 wherein [HET = heterocycle; R3 = (C1-C10)alkyl, etc.; R4 = H, (C1-C6)alkyl, (C3-C7)cycloalkyl; or R3 and R4 form (C5-C7)cycloalkyl, etc.; X4 = H, (C1-C6)alkyl; or X4 and R4 form 5-7-member ring; R6 = bond, -Z1(CH2)aC(X)5(X5a)(CH2)b-, etc.; a, b = 0-3; X5, X5a = H, CF3, etc.; Z1 = bond, O, NX2, provided that when a and b are both 0 then Z1 is not NX2 or O; R7 and R8 = H, (substituted)(C1-C6)alkyl, etc.]), a **prodrug** thereof or a pharmaceutically acceptable salt of said secretagogue or said **prodrug**. In a double-blind, placebo-controlled, multiple dose evaluation of 2-amino-N-[2-[3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxoethyl]isobutyramide, L-tartrate in calorically restricted obese men and women, **testosterone** level appeared to influence the response to growth hormone secretagogue.

L2 ANSWER 10 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:117794 HCAPLUS  
DOCUMENT NUMBER: 138:153537  
TITLE: Preparation of imidazole-containing heterobicyclic  
modulators of androgen receptor function  
INVENTOR(S): Sun, Chongqing; Robl, Jeffrey A.; Salvati, Mark E.;  
Wang, Tammy; Hamann, Lawrence; Augeri, David  
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA  
SOURCE: PCT Int. Appl., 99 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011824	A1	20030213	WO 2002-US24185	20020731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,  
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,  
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG

US 2003055094 A1 20030320 US 2002-209461 20020731

US 6670386 B2 20031230

EP 1414795 A1 20040506 EP 2002-756813 20020731

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

US 2004092559 A1 20040513 US 2003-685020 20031014

PRIORITY APPLN. INFO.:

US 2001-309059P P 20010731

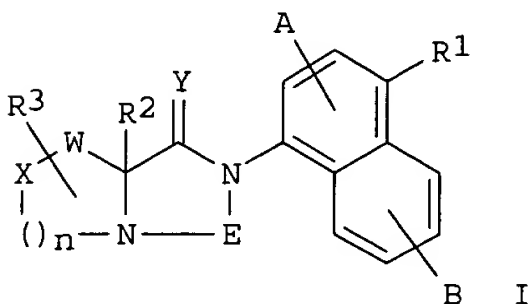
US 2002-209461 A3 20020731

WO 2002-US24185 W 20020731

OTHER SOURCE(S):

MARPAT 138:153537

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AB The invention provides imidazole-containing heterobicyclic compds. (shown as I, including all **prodrug** esters, pharmaceutically acceptable salts and stereoisomers thereof; variables defined below; e.g. tetrahydro-2-(4-nitro-1-naphthalenyl)imidazo[1,5-a]pyridine-1,3(2H,5H)-dione), methods of using such compds. for the treatment of nuclear hormone receptor-associated conditions, such as age related diseases, for example sarcopenia, and pharmaceutical compns. containing such compds. Pharmacol. assay procedures are described but results for I are not reported. For I: R1 = H, cyano, nitro, halo, heterocyclo, OR4, CO2R5, CONHR5, COR5, S(O)mR5, SO2NR5R5', NHCOR5 and NHSO2R5; R2 = H, alkyl or substituted alkyl, (un)substituted alkenyl, (un)substituted arylalkyl, CO2R5, CONR5R5' and CH2OR5; R3 = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, (un)substituted cycloalkyl, (un)substituted arylalkyl, (un)substituted heterocycloalkyl, (un)substituted aryl, (un)substituted heteroaryl, halo, cyano, NHCOR5, NHCO2R5, NHCONR5R5', NHSO2R5 and OR4. R4 = H, (un)substituted alkyl, CHF2, CF3 and COR5; R5 and R5' = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, (un)substituted cycloalkyl, (un)substituted heterocycloalkyl, (un)substituted arylalkyl, (un)substituted aryl, (un)substituted heteroaryl and cyano; W = (CR6R6')m, CHOH(CR6R6')m, CO(CR6R6')m and C:NOR4(CR6R6')m. R6 and R6' = H, (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, (un)substituted cycloalkyl, (un)substituted arylalkyl, (un)substituted heterocycloalkyl, (un)substituted aryl, (un)substituted heteroaryl, halo, cyano, NHCOR5, NHCO2R5, NHCONR5R5', NHSO2R5 and OR4; X = methylene, O, S(O)m, NCOR5,

NCO2R5, NCONHR5R5', NSO2NR5R5'; Y = O, S and H2; E = C:Z, CHR5, SO2, P(O)R5 and P(O)OR5; Z = O, S, NH and NR5; A and B = H, halo, cyano, nitro, (un)substituted alkyl and OR4; m = 0-2; and n = 1-2;. Although the methods of preparation are not claimed, 42 example preps. are included.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:977668 HCAPLUS

DOCUMENT NUMBER: 138:61309

TITLE: Enhanced steroidal drug delivery in transdermal systems

INVENTOR(S): Houze, David; Nguyen, Viet

PATENT ASSIGNEE(S): Noven Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 49 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002102390	A1	20021227	WO 2002-US16579	20020618
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1406633	A1	20040414	EP 2002-749537	20020618
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
BR 2002010516	A	20041005	BR 2002-10516	20020618
JP 2005500299	T2	20050106	JP 2003-504976	20020618
US 2003152613	A1	20030814	US 2002-330279	20021230
US 2003152614	A1	20030814	US 2002-330360	20021230
US 2003152615	A1	20030814	US 2002-330361	20021230
US 2003232073	A1	20031218	US 2002-330281	20021230
PRIORITY APPLN. INFO.:			US 2001-298381P	P 20010618
			US 2001-948107	A 20010907
			WO 2002-US16579	W 20020618

AB A composition for transdermal administration resulting from an admixt. includes a therapeutically effective amount of a drug that includes a parent drug and a **prodrug** and a carrier, wherein the parent drug and **prodrug** are individually present in an amount sufficient for a pharmacol. effect. The admixt. include: a therapeutically effective amount of a steroid and a steroid derivative and a carrier for the steroid. The steroid and the corresponding derivative are present in a weight ratio of 10:1 to

1:10 steroid-corresponding steroid derivative In a preferred embodiment ratio is 6:1 to 1:6. In a preferred embodiment, the corresponding steroid derivative is a steroidal ester. In another preferred embodiment, the carrier is a polymer that includes a pressure-sensitive adhesive. In another preferred embodiment, the parent drug is an ACE inhibitor such as ramipril

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and the **prodrug** is an ACE inhibitor **prodrug** such as ramipril Et and/or Me esters. Thus, a transdermal delivery system contained norethindrone 1.2, estradiol 0.9, norethindrone acetate 2.5, VA-64 15.0, GMS-737 (acrylic PSA), oleic acid 3.0, dipropylene glycol 9.0, and Bio-PSA-7-4603 63.4%.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:883250 HCAPLUS

DOCUMENT NUMBER: 139:78567

TITLE: Adenovirus Mediated Prostate Specific Enzyme **Prodrug** Gene Therapy Using Prostate Specific Antigen Promoter Enhanced by the Cre-loxP System

AUTHOR(S): Yoshimura, Ichiro; Ikegami, Shusei; Suzuki, Satoshi; Tadakuma, Takushi; Hayakawa, Masamichi

CORPORATE SOURCE: Departments of Urology and Parasitology and Immunology, National Defense Medical College, Tokorozawa, Saitama, Japan

SOURCE: Journal of Urology (Hagerstown, MD, United States) (2002), 168(6), 2659-2664

CODEN: JOURAA; ISSN: 0022-5347

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB PURPOSE: Tissue or tumor specific gene delivery is crucial for achieving successful results in suicide gene therapy. Prostate specific antigen (PSA) promoter is known to be highly specific in prostate tissue but its promoter activity is much weaker than that of constitutive viral promoters. In the current study we enhanced PSA promoter activity by combining it with the Cre-loxP system. We also applied this system to adenovirus mediated suicide gene therapy with the cytosine deaminase (CD) gene. MATERIALS AND METHODS: The Cre-loxP DNA recombination system was used to enhance PSA promoter. A plasmid with the PSA promoter-enhancer combination was constructed to drive Cre recombinase. Another plasmid contained the cytomegalovirus promoter-loxP-flanked stop signal-luciferase gene. LNCaP human prostate cancer cells were co-transfected with these 2 plasmids and luciferase activity was measured to assess promoter activities. Adenoviral vectors with the CD suicide gene were constructed in similar fashion and tested in LNCaP cells in in vitro/in vivo prostate cancer models. RESULTS: Promoter activity of the combined PSA promoter/enhancer and Cre-loxP system was 3 times stronger than that of PSA promoter/enhancer alone. It was further enhanced 7-fold in the presence of **testosterone**. Application of this system to CD suicide gene therapy by adenoviral vectors inhibited s.c. LNCaP tumor growth in nude mice. CONCLUSIONS: Combining the Cre-loxP system with PSA promoter/enhancer amplified promoter activity and was found to inhibit the growth of PSA producing prostate cancer cells in vivo.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:551606 HCAPLUS

DOCUMENT NUMBER: 137:99033

TITLE: Water soluble amine esters of **testosterone** for intranasal administration

INVENTOR(S): Hussain, Anwar A.

PATENT ASSIGNEE(S): University of Kentucky, USA

SOURCE: U.S., 8 pp.

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CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6423701	B1	20020723	US 1996-591767	19960125
PRIORITY APPLN. INFO.:			US 1996-591767	19960125

OTHER SOURCE(S): MARPAT 137:99033

AB The present invention provides novel water soluble **testosterone** analogs. These **testosterone** analogs are suitable for intranasal administration to patients requiring increased plasma **testosterone** levels. The present invention also provides pharmaceutical compns. containing the **testosterone** analogs of the present invention. The present invention further provides a method of increasing plasma **testosterone** levels in patients in need of such treatment comprising the intranasal administration of the water-soluble **testosterone** analogs and pharmaceutical compns. of the present invention.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:426631 HCAPLUS

DOCUMENT NUMBER: 137:16062

TITLE: Combination for treating andropause and related conditions containing estrogen agonists/antagonists and **testosterone**

INVENTOR(S): McLean, David Burton

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: Eur. Pat. Appl., 43 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

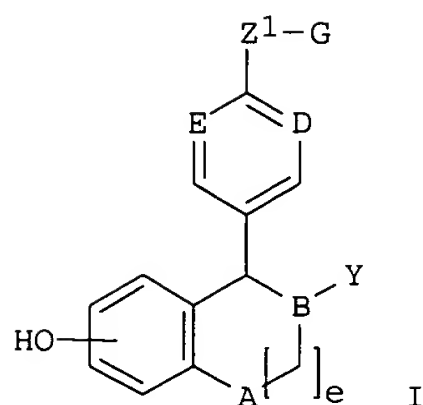
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1210951	A2	20020605	EP 2001-309457	20011108
EP 1210951	A3	20030924		
EP 1210951	B1	20050202		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
AT 288303	E	20050215	AT 2001-309457	20011108
US 2002115676	A1	20020822	US 2001-995130	20011127
CA 2363935	AA	20020530	CA 2001-2363935	20011128
AU 2001095165	A5	20020606	AU 2001-95165	20011129
ZA 2001009836	A	20030529	ZA 2001-9836	20011129
NZ 515822	A	20030530	NZ 2001-515822	20011129
JP 2002193809	A2	20020710	JP 2001-365803	20011130
PRIORITY APPLN. INFO.:			US 2000-250071P	P 20001130

OTHER SOURCE(S): MARPAT 137:16062

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AB The present invention concerns the treatment of andropause and related conditions using a combination of an estrogen agonist/antagonist and **testosterone**. The Markush structure for the estrogen agonist/antagonist is I, where A = CH<sub>2</sub> or NR; B, D, and E = CH or N; Y = a ring; Z<sub>1</sub> is linear or part of a ring with G; and G is a linear or a ring. The specifically claimed estrogen agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a **prodrug** thereof. Drugs containing the compds. of the invention can be used to treat gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis; or increasing libido; or maintaining or improving vascular reactivity in a male patient. A treatment kit containing (a) one or more pharmaceutical compns. comprising an estrogen agonist/antagonist and **testosterone**; and (b) instructions for administering the pharmaceutical composition is also claimed.

L2 ANSWER 15 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 2002:314394 HCAPLUS  
 DOCUMENT NUMBER: 136:335264  
 TITLE: Use of an estrogen agonists and antagonists for assessment, improvement, or maintenance of urogenital health  
 INVENTOR(S): Day, Wesley Warren; Lee, Andrew George; Thompson, David Duane  
 PATENT ASSIGNEE(S): Pfizer Products Inc., USA  
 SOURCE: Eur. Pat. Appl., 52 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1199069	A2	20020424	EP 2001-308625	20011009
EP 1199069	A3	20031119		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2358938	AA	20020416	CA 2001-2358938	20011012
US 2002128276	A1	20020912	US 2001-976825	20011012
JP 2002179593	A2	20020626	JP 2001-316248	20011015
ZA 2001008443	A	20030415	ZA 2001-8443	20011015

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NZ 514821	A	20040130	NZ 2001-514821	20011015
US 2003125319	A1	20030703	US 2002-292203	20021112
PRIORITY APPLN. INFO.:			US 2000-240789P	P 20001016
			US 2001-976825	A3 20011012

OTHER SOURCE(S): MARPAT 136:335264

AB The invention relates to methods and kits useful for the improvement, or maintenance urogenital health using an estrogen agonist/antagonist compds. (Markush structures are included). The methods of treatment are effective for improving or maintaining urogenital health while substantially reducing the concomitant liability of adverse effects associated with estrogen administration. This invention also relates to methods of assessing vaginal health.

L2 ANSWER 16 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:248837 HCAPLUS

DOCUMENT NUMBER: 137:299709

TITLE: **Testosterone** 17 $\beta$ -N,N-dimethylglycinate hydrochloride: a **prodrug** with a potential for nasal delivery of **testosterone**

AUTHOR(S): Hussain, Anwar A.; Al-Bayatti, Ansam A.; Dakkuri, Adnan; Okochi, Kazuhiro; Hussain, Munir A.

CORPORATE SOURCE: College of Pharmacy, University of Kentucky, Lexington, KY, 40536-0082, USA

SOURCE: Journal of Pharmaceutical Sciences (2002), 91(3), 785-789

CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study was to examine the potential of the nasal route for the systemic delivery of the poorly water-soluble drug **testosterone** (TS) using a water-soluble **prodrug**, TS 17 $\beta$ -N,N-dimethylglycinate hydrochloride. The physicochem. properties of the **prodrug**, in vitro hydrolysis in human liver homogenate, and in vivo nasal and i.v. expts. were performed in rats. The aqueous solubility of the **prodrug** was more than 100 mg/mL, compared with 0.01 mg/mL for TS, and its log partition coefficient between 0.05 M, phosphate buffer (pH 6) and octanol was 2.4. The **prodrug** was found to generate TS in 33% human liver homogenate and was absorbed from the nasal cavity rapidly and quant. The bioavailabilities of both the **prodrug** and TS after nasal administration of the **prodrug** were similar to that after equivalent i.v. doses. These studies in rats suggest that this water-soluble **prodrug** of TS may have therapeutic utility for the management of TS deficiency.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 17 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:885822 HCAPLUS

DOCUMENT NUMBER: 136:25103

TITLE: Sulfonamide group-containing pharmaceutical prodrugs

INVENTOR(S): Elger, Walter; Hillisch, Alexander; Hedden, Annemarie; Schwarz, Sigfrid; Schoellkopf, Klaus

PATENT ASSIGNEE(S): Jenapharm GmbH & Co. KG, Germany

SOURCE: PCT Int. Appl., 27 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

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FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001091797	A2	20011206	WO 2001-EP5169	20010508
WO 2001091797	A3	20020620		
W: AE, AG, AU, BA, BB, BG, BR, CA, CN, CO, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LS, MA, MG, MN, MX, NO, NZ, PL, SG, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10027887	A1	20011213	DE 2000-10027887	20000531
CA 2410630	AA	20021128	CA 2001-2410630	20010508
EP 1294402	A2	20030326	EP 2001-943329	20010508
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
BR 2001011294	A	20030610	BR 2001-11294	20010508
JP 2003534386	T2	20031118	JP 2001-587809	20010508
NO 2002005739	A	20021129	NO 2002-5739	20021129
BG 107556	A	20040130	BG 2003-107556	20030214
US 2004014781	A1	20040122	US 2003-296973	20030801
PRIORITY APPLN. INFO.:			DE 2000-10027887	A 20000531
			WO 2001-EP5169	W 20010508

OTHER SOURCE(S): MARPAT 136:25103

AB The invention relates to compds. which, acting as a **prodrug** and/or support, enable an active agent to be taken up by the erythrocytes and/or an active agent to bind to the erythrocytes. The uptake of these compds. by and/or the binding thereof to the erythrocytes is made possible by a group of formula -SO<sub>2</sub>NR<sub>1</sub>R<sub>2</sub>, wherein R<sub>1</sub> and R<sub>2</sub>, independently of each other, is H, acyl, alky, cycloalkyl group, aryl, cyano or a hydroxy group. The inventive prodrugs enable active agents such as endogenic substances, natural substances and synthetic substances with therapeutically useful properties which have a high "first path" effect, to be administered orally effectively or significantly improve the oral activity. The sepharose-immobilized estradiol sulfamate was found to bind to carbonic anhydrase II in erythrocytes.

L2 ANSWER 18 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:845768 HCAPLUS

DOCUMENT NUMBER: 137:68023

TITLE: **Testosterone** delivery using glutamide-based complex high axial ratio microstructures

AUTHOR(S): Goldstein, Alex S.; Amory, John K.; Martin, Stephanie M.; Vernon, Chris; Matsumoto, Alvin; Yager, Paul

CORPORATE SOURCE: Departments of Chemistry and Biochemistry, University of Washington, Seattle, WA, 98195-1700, USA

SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(11), 2819-2825

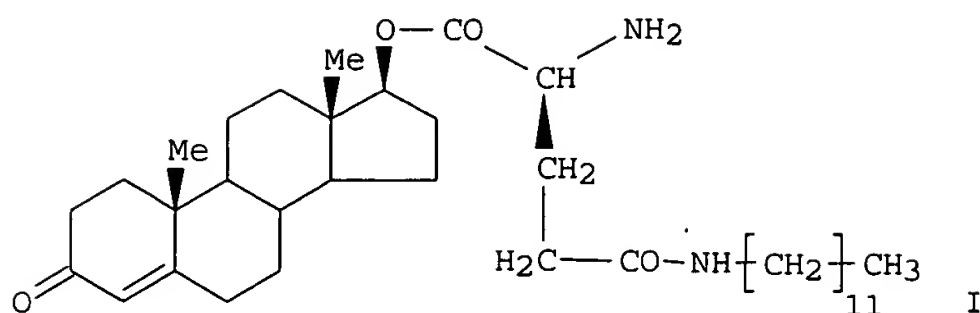
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

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AB Complex high axial ratio microstructures (CHARMs such as I) were evaluated for delivery of **testosterone** in vivo. Methods to incorporate **testosterone** included noncovalent mixing and covalent attachment of **testosterone** to the lipid to form a **prodrug** monomer. When prepared by covalent attachment, **testosterone**-loaded CHARMs were resistant to in vitro spontaneous hydrolysis; when injected into rats, **testosterone** was released with biphasic kinetics consisting of a burst followed by a much slower phase. Some CHARM material associated with **testosterone** persisted at the site of injection for at least 9 days.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:564841 HCAPLUS

DOCUMENT NUMBER: 135:132470

TITLE: Selective estrogen receptor modulators in combination with estrogens for therapeutic use

INVENTOR(S): Labrie, Fernand

PATENT ASSIGNEE(S): Endorecherche, Inc., Can.

SOURCE: PCT Int. Appl., 160 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

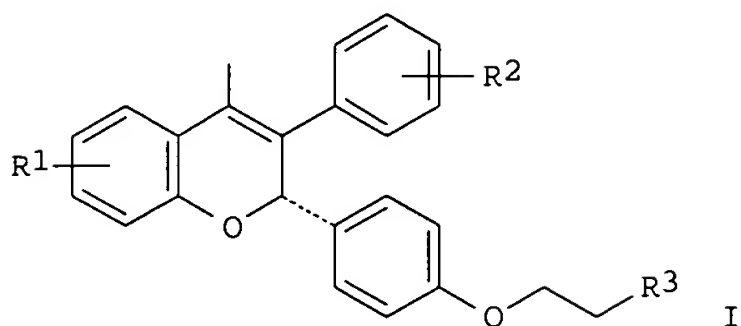
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001054699	A1	20010802	WO 2001-CA86	20010126
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AA	20010802	CA 2001-2395730	20010126
	A1	20021030	EP 2001-902194	20010126
			DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, V, FI, RO, MK, CY, AL, TR	
	A	20030311	BR 2001-8107	20010126
	T2	20030708	JP 2001-554683	20010126
	A1	20021226	US 2001-52803	20011107
	A1	20030227	US 2001-52824	20011107

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US 2003065008	A1	20030403	US 2002-143894	20020509
NO 2002003484	A	20020722	NO 2002-3484	20020722
ZA 2002005926	A	20030724	ZA 2002-5926	20020724
PRIORITY APPLN. INFO.:			US 2000-178601P	P 20000128
			US 2001-771180	A1 20010126
			WO 2001-CA86	W 20010126

OTHER SOURCE(S): MARPAT 135:132470  
GI



AB Methods for reduction or elimination of the incidence of hot flashes and menopausal symptoms, while decreasing the risk of acquiring breast or endometrial cancer and furthermore treating and/or inhibiting the development of osteoporosis, hypercholesterolemia, hyperlipidemia, atherosclerosis, hypertension, insulin resistance, diabetes, loss of muscle mass, obesity, irregular menstruation, Alzheimer's disease, or vaginal dryness in susceptible warm-blooded animals, including humans, involves administration of selective estrogen receptor modulators, particularly compds. I (R1, R2 = OH, moiety convertible to OH in vivo; R3 = (un)saturated (substituted) pyrrolidiny, (un)saturated (substituted) piperidiny, etc.) and an amount of an estrogen or mixed estrogenic/androgenic compound Further administration of bisphosphonates, or a sex steroid precursor is specifically disclosed for the medical treatment and/or inhibition of development of some of these above-mentioned diseases. Pharmaceutical compns. for delivery of active ingredient(s) and kit(s) useful to the invention are also disclosed.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:435015 HCAPLUS

DOCUMENT NUMBER: 135:33380

TITLE: Benzyl tetralins, formulations and uses thereof as inhibitors of 17 $\beta$ -hydroxy steroid dehydrogenase for treatment of androgen- and estrogen-mediated diseases

INVENTOR(S): Smith, Harold John; Mason, Peter; Ahmadi, Masoud; Nicholls, Paul Joseph; Greer, Valerie

PATENT ASSIGNEE(S): University College Cardiff Consultants Limited, UK

SOURCE: PCT Int. Appl., 44 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001042181	A1	20010614	WO 2000-GB4700	20001208
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,				
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,				
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,				
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,				
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

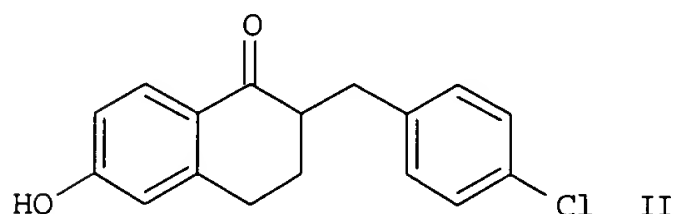
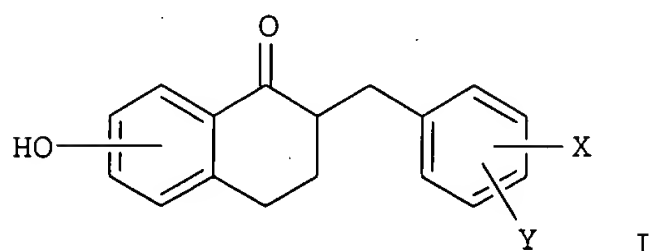
GB 1999-29302

A 19991210

OTHER SOURCE(S):

MARPAT 135:33380

GI



AB A benzyl tetralin I or a pharmaceutically acceptable salt or **prodrug** thereof is disclosed [wherein X = halogen, C1-6 alkyl (optionally substituted by at least one halogen), a fused bicyclic hydrophobic ring system, or Ph (optionally substituted by at least one halogen); Y = H or halogen; or X and Y together form the residue of a carbocyclic ring]. I are useful as inhibitors of 17 $\beta$ -hydroxy steroid dehydrogenase (17 $\beta$ -HSD) isoforms operable in the steroidogenesis pathway, and have therapeutic applications in the treatment of androgen- or estrogen-dependent or mediated diseases. In particular, I are useful for treating prostate cancer or breast cancer. I may be formulated with other steroidogenesis pathway enzyme inhibitors, where the inhibited enzyme is a 17 $\beta$ -HSD isoform, 5 $\alpha$ -steroid reductase, aromatase P450arom, or estrogen sulfatase. Eight specific examples and their intermediates are described. For instance, 6-methoxy-3,4-dihydronaphthalen-1(2H)-one underwent a sequence of O-demethylation (57%), O-protection as the THP ether (86.8%), condensation with 4-chlorobenzaldehyde to give a 2-benzylidene derivative (51.7%), deprotection (94%), and hydrogenation of the benzylidene bond (69.5%), to give title compound II. This compound at 200  $\mu$ M gave 97.9% inhibition of androstenedione reduction by human testicular microsomal 17 $\beta$ -HSD in vitro, and 59.6% inhibition of estrone reduction by human placental cytosolic 17 $\beta$ -HSD in vitro.

REFERENCE COUNT:

2

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 16:42:20 ON 26 APR 2005)

FILE 'STNGUIDE' ENTERED AT 16:42:25 ON 26 APR 2005

FILE 'HCAPLUS' ENTERED AT 16:42:37 ON 26 APR 2005

L1 57193 S TESTOSTERONE  
L2 48 S L1 AND PRODRUG  
L3 6 S L2 AND ETHER  
L4 17 S L2 AND ESTER

=> d 12 35-48 ibib hitstr abs

L2 ANSWER 35 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1994:235356 HCAPLUS  
DOCUMENT NUMBER: 120:235356  
TITLE: Use of Caco-2 cells as an in vitro intestinal  
absorption and metabolism model  
AUTHOR(S): Gan, Liang Shang; Eads, Cindy; Niederer, Tara;  
Bridgers, Avis; Yanni, Souzan; Hsyu, Poe Hrr;  
Pritchard, Fred J.; Thakker, Dhiren  
CORPORATE SOURCE: Dep. Drug Metabolism, Glaxo Inc. Res. Inst., Research  
Triangle Park, NC, 27709, USA  
SOURCE: Drug Development and Industrial Pharmacy (1994),  
20(4), 615-31  
CODEN: DDIPD8; ISSN: 0363-9045  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB The Caco-2 cell line, a human colorectal carcinoma cell line, is an  
established in vitro model for the study of drug transport in the human  
intestine. The authors have routinely utilized this in vitro model to 1)  
elucidate intestinal absorption mechanisms of small drug mols. and  
peptide-like therapeutic agents (e.g. paracellular/transcellular passive  
diffusion and carrier-mediated active transport), 2) screen and select  
orally active therapeutic agents, 3) identify optimum luminal pH's for  
drug absorptions, 4) address dissoln. rate-related absorption problems, 5)  
assess mucosal toxicity of therapeutic agents, and 6) evaluate  
**prodrug** approaches for enhanced drug absorptions. The authors  
have also utilized this in vitro model to assess the metabolic stability  
of therapeutic agents in the intestinal epithelium. demonstrated in this  
report are primarily the techniques for the elucidation of absorption  
mechanisms. Examples of the characterization of  
paracellular/transcellular passive diffusion pathways and carrier-mediated  
active transport will be given. Application of the Caco-2 model to the  
process of drug development will also be discussed.

L2 ANSWER 36 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1993:197944 HCAPLUS  
DOCUMENT NUMBER: 118:197944  
TITLE: Testosteronyl 4-dimethylaminobutyrate·hydrochlo  
ride: a **prodrug** with improved skin  
penetration rate  
AUTHOR(S): Milosovich, Susan; Hussain, Anwar; Dittert, Lewis;  
Aungst, Bruce; Hussain, Munir  
CORPORATE SOURCE: SmithKline Beecham Pharm., King of Prussia, PA,  
19406-0939, USA  
SOURCE: Journal of Pharmaceutical Sciences (1993), 82(2),

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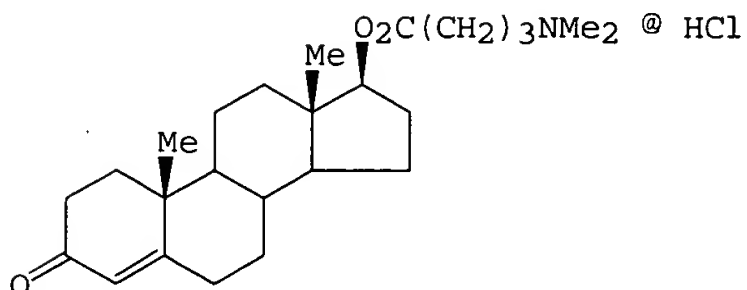
DOCUMENT TYPE:

Journal

LANGUAGE:

English

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AB Testosteronyl 4-dimethylaminobutyrate-HCl (I) **prodrug** has a lipophilic portion and a tertiary amine group that exists in the protonated form at physiol. pH, making it more permeable through the skin. I penetration through the mice skin was 7-fold higher than that of the parent compound, **testosterone** (.apprx.140 and .apprx.20 ng/mL, resp.).

L2 ANSWER 37 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1992:455767 HCAPLUS

DOCUMENT NUMBER: 117:55767

TITLE: The in vitro enzymic labilities of chemically distinct phosphomonoester prodrugs

AUTHOR(S): Kearney, Albert S.; Stella, Valentino J.

CORPORATE SOURCE: Dep. Pharm. Chem., Univ. Kansas, Lawrence, KS, 66045, USA

SOURCE: Pharmaceutical Research (1992), 9(4), 497-503

CODEN: PHREEB; ISSN: 0724-8741

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The kinetics of decomposition of phosphomonoesters of hydroxymethyl-5,5-diphenylhydantoin (I), estrone (II), 17 $\beta$ - **testosterone** (III), 1-phenylvinyl alc. (IV), and 17 $\alpha$ - **testosterone** (V) were studied in rat whole blood at 25 and(or) 37°. As the acidity of the leaving hydroxyl group of the phosphomonoester increased, there was a tendency for the rate of hydrolysis to increase, except for the anomalous behavior of IV, which was consistent with its relative rate of hydrolysis in aqueous solns. In addition, the kinetics of hydrolysis of I-V and p-nitrophenyl phosphate (p-NPP) were studied in the presence of isolated alkaline phosphatases from a variety of sources. The initial rate of production of 17 $\alpha$ - and 17 $\beta$ - **testosterone** from their resp. phosphate esters, V and III, in the presence of human placental alkaline phosphatase, revealed that III was hydrolyzed 5.3-fold more rapidly than V. This difference in reactivity might have been the result of differences in the stereochem. and(or) steric nature of the 2 isomers. For p-NPP, I, II, and IV, the kcat and kcat/Km values determined in the presence of the various alkaline phosphatases showed little variation, whereas for III, the catalytic consts., kcat and kcat/Km, were dramatically less than those found for p-NPP, I, II, and IV. This suggested that the reaction steps, involving the noncovalent binding of the phosphomonoester

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to the enzyme and(or) the nucleophilic displacement of the leaving alc. of the phosphomonoester by the reactive amino acid residue of the enzyme, might have been less favorable in the case of III, where the C atom of the ester linkage was secondary and was associated with a rigid ring system.

L2 ANSWER 38 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1992:449157 HCAPLUS

DOCUMENT NUMBER: 117:49157

TITLE: Preparation of brain-targeted acyloxymethylphosphonate prodrugs

INVENTOR(S): Bodor, Nicholas S.

PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 179 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

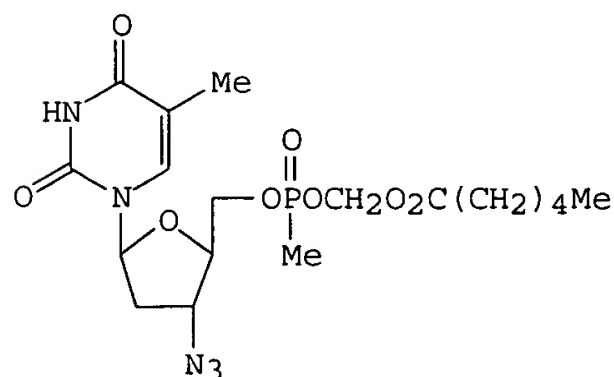
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9200988	A1	19920123	WO 1991-US4824	19910712
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MN, MW, NL, NO, PL, RO, SD, SE, SU				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
US 5177064	A	19930105	US 1990-553548	19900713
CA 2087194	AA	19920114	CA 1991-2087194	19910712
AU 9183000	A1	19920204	AU 1991-83000	19910712
AU 649466	B2	19940526		
EP 539493	A1	19930505	EP 1991-913701	19910712
EP 539493	B1	19970326		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05509313	T2	19931222	JP 1991-513064	19910712
AT 150759	E	19970415	AT 1991-913701	19910712
US 5413996	A	19950509	US 1992-962504	19921016
US 5618803	A	19970408	US 1994-340896	19941115
PRIORITY APPLN. INFO.:			US 1990-553548	A 19900713
			WO 1991-US4824	A 19910712
			US 1992-962504	A3 19921016

OTHER SOURCE(S): MARPAT 117:49157  
GI



AB QP(O)(R1)OCHR2O2CR3 [Q = O-bonded drug moiety; R1 = alkyl, aryl, aralkyl; R2 = H, hetero)aryl, (cyclo)alkyl, heterocyclyl, aralkyl; R3 = alkyl,

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alkenyl, (alkyl)cycloalkyl(alkyl), aryloxyalkyl, pyridyl, (substituted) Ph, phenylalkyl], were prepared Thus, zidovudine was stirred with MeP(O)Cl<sub>2</sub> and Na<sub>2</sub>CO<sub>3</sub> in acetone for 17 h; H<sub>2</sub>O was added to give 31.3% zidovudine methylphosphonate (I), which was treated with iodomethyl hexanoate and CsF in DMF to give title compound II. Title compds. are rapidly hydrolyzed in vivo, and I was found in the brain after administration of II.

L2 ANSWER 39 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1991:228552 HCAPLUS

DOCUMENT NUMBER: 114:228552

TITLE: Preparation of (aminoalkyl)phenylacyl-derivatized drugs with improved solution stability and solubility

INVENTOR(S): Bundgaard, Hans; Falch, Erik

PATENT ASSIGNEE(S): Den.

SOURCE: PCT Int. Appl., 109 pp.

CODEN: PIXXD2

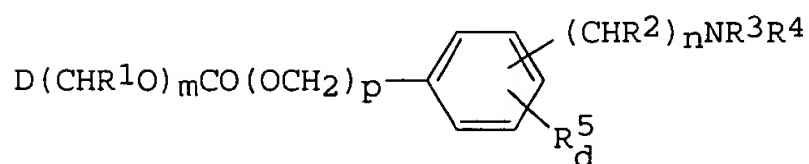
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9008128	A1	19900726	WO 1990-DK20	19900119
W: AU, CA, FI, JP, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
CA 2045591	AA	19900721	CA 1990-2045591	19900119
AU 9050323	A1	19900813	AU 1990-50323	19900119
EP 454773	A1	19911106	EP 1990-902624	19900119
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 04502918	T2	19920528	JP 1990-502553	19900119
PRIORITY APPLN. INFO.:			DK 1989-240	A 19890120
			WO 1990-DK20	A 19900119
OTHER SOURCE(S):		MARPAT 114:228552		
GI				



AB The title compds. [I; D = residue of an NH- or OH-containing drug; R<sup>1</sup> = H, alkyl, aryl, aralkyl, alkoxy carbonyl, carbamoyl; R<sup>2</sup> = H, alkyl; R<sup>3</sup>, R<sup>4</sup> = H, (substituted) alkyl, aralkyl, alkenyl, cycloalkyl; R<sup>3</sup>R<sup>4</sup>N = (substituted) heterocyclyl; R<sup>5</sup> = halo, OH, alkyl, alkoxy; d = 0-4; m, p = 0, 1; n = 1-4] were prepared as prodrugs having improved stability in aqueous solution Thus, hydrocortisone in CH<sub>2</sub>Cl<sub>2</sub> was stirred with Et<sub>3</sub>N and 3-ClCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COCl to give hydrocortisone 21-(3-chloromethyl)benzoate. The latter was stirred with NaI and N-methylpiperazine in Me<sub>2</sub>CO at 60° to give hydrocortisone 21-[3-(4-methylpiperazin-1-yl)methyl]benzoate, converted to the dihydrochloride. The latter had solubility of 3.5 mg/mL in H<sub>2</sub>O at 21°, vs. 0.40 mg/mL for hydrocortisone itself. I are preferably stored at pH 3-5. I derivs. of hydrocortisone showed t<sub>1/2</sub> of



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8-147 min in human plasma at pH 7.4.

L2 ANSWER 40 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1991:88647 HCAPLUS

DOCUMENT NUMBER: 114:88647

TITLE: Preparation of cyclodextrin derivatives for active agent delivery as inclusion complexes and for separating racemic mixtures

INVENTOR(S): Lincoln, Stephen Frederick; Coates, John Hewlett; Easton, Christopher John; Van Eyk, Stephen John; May, Bruce Lindly; Singh, Paramjit; Williams, Michael Lloyd; Stile, Martyn Allen

PATENT ASSIGNEE(S): Australian Commercial Research and Development Ltd., Australia

SOURCE: PCT Int. Appl., 118 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9002141	A1	19900308	WO 1989-AU359	19890823
W: AU, BB, BG, BR, DK, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 8944290	A1	19900323	AU 1989-44290	19890823
AU 693072	B2	19980625		
EP 431080	A1	19910612	EP 1989-911240	19890823
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
BR 8907625	A	19910820	BR 1989-7625	19890823
JP 04500229	T2	19920116	JP 1989-510576	19890823
CN 1040987	A	19900404	CN 1989-106650	19890830
DD 297833	A5	19920123	DD 1989-332260	19890831
ZA 8906624	A	19920129	ZA 1989-6624	19900830
US 5324750	A	19940628	US 1992-979451	19921120

PRIORITY APPLN. INFO.:

AU 1988-165	A	19880831
AU 1988-189	A	19880901
AU 1988-618	A	19880927
AU 1988-1053	A	19881019
AU 1988-1198	A	19881027
AU 1988-1417	A	19881111
AU 1989-4894	A	19890626
AU 1989-4909	A	19890626
AU 1989-5034	A	19890703
AU 1989-5278	A	19890717
AU 1989-5354	A	19890719
AU 1989-5576	A	19890803
AU 1989-5641	A	19890807
AU 1989-5682	A	19890809
WO 1989-AU359	A	19890823
US 1991-684888	B1	19910412

AB Cyclodextrin derivs. are prepared, which form soluble and stable inclusion complexes and covalently-bonded compds. with drugs, pesticides and cosmetics. The cyclodextrin derivs. have  $\geq 1$  NH<sub>2</sub> group substituted with OH at C-2, C-3, or C-6. 6A-O-p-Toluenesulfonyl- $\beta$ -cyclodextrin prepared as usual, was treated with Na azide and 1,1,2,2-tetrachloroethane,

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to give 6A-azido-6A-deoxy- $\beta$ -cyclodextrin, which was hydrogenated over Pd black, in water, to yield 6A-amino-6A-deoxy- $\beta$ -cyclodextrin. This was treated with ibuprofen anhydride to give 6A-deoxy-6A-( $\alpha$ -methyl-4-isobutylphenylacetamido)- $\beta$ -cyclodextrin, a **prodrug** for ibuprofen delivery. The cyclodextrin derivs. and their inclusion complexes may also be used for the chromatog. separation of enantiomers from racemic mixts.

L2 ANSWER 41 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1990:104779 HCAPLUS  
DOCUMENT NUMBER: 112:104779  
TITLE: The utilization of prodrugs to enhance transdermal penetration of **testosterone**, deoxycorticosterone, and indomethacin  
AUTHOR(S): Milosovich, Susan Marie  
CORPORATE SOURCE: Univ. Kentucky, Lexington, KY, USA  
SOURCE: (1988) 191 pp. Avail.: Univ. Microfilms Int., Order No. DA8914912  
From: Diss. Abstr. Int. B 1989, 50(4), 1428  
DOCUMENT TYPE: Dissertation  
LANGUAGE: English  
AB Unavailable

L2 ANSWER 42 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1990:7383 HCAPLUS  
DOCUMENT NUMBER: 112:7383  
TITLE: Preparation of dihydropyridine-containing prodrugs for brain-specific drug delivery  
INVENTOR(S): Bodor, Nicholas S.  
PATENT ASSIGNEE(S): University of Florida, USA  
SOURCE: U.S., 282 pp. Cont.-in-part of U.S. 4,479,932.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 7  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 4824850	A	19890425	US 1984-665940	19841029
US 4479932	A	19841030	US 1982-379316	19820518
US 4622218	A	19861111	US 1983-475493	19830315
EP 218300	A2	19870415	EP 1986-201710	19830512
EP 218300	A3	19880928		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 221588	A2	19870513	EP 1986-201711	19830512
EP 221588	A3	19880921		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 222425	A2	19870520	EP 1986-201714	19830512
EP 222425	A3	19880921		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 224283	A2	19870603	EP 1986-201713	19830512
EP 224283	A3	19880921		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 256577	A2	19880224	EP 1987-201385	19830512
EP 256577	A3	19880706		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
EP 262696	A2	19880406	EP 1987-201384	19830512
EP 262696	A3	19880720		

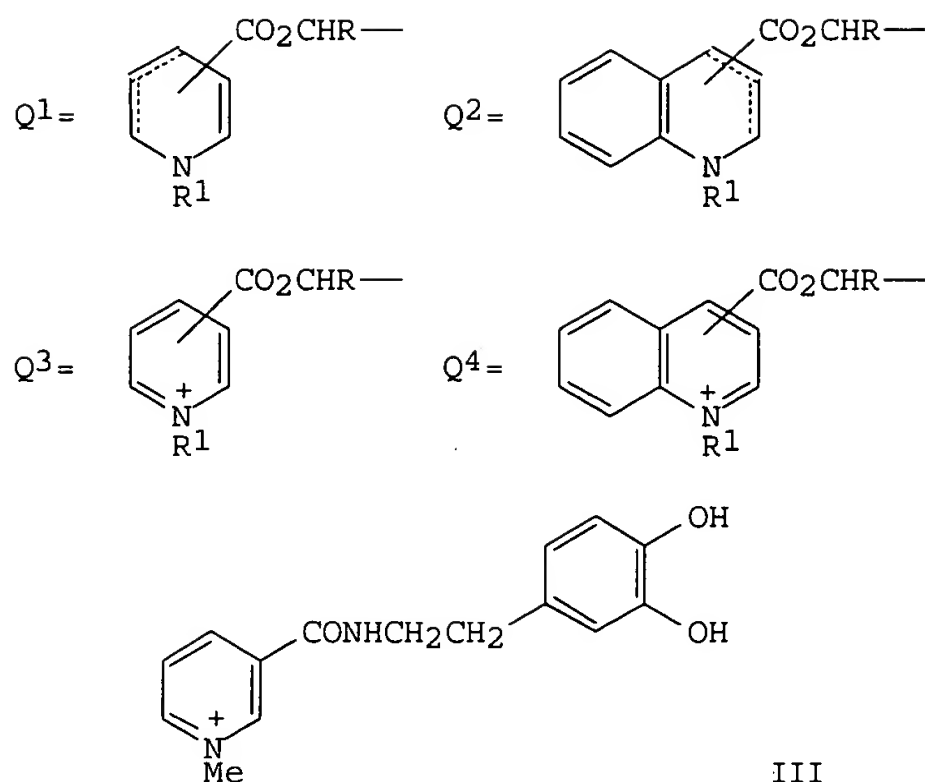
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R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
CA 1253856	A1	19890509	CA 1983-428192	19830516
ZA 8303521	A	19841224	ZA 1983-3521	19830517
US 4540564	A	19850910	US 1983-516382	19830722
US 4727079	A	19880223	US 1985-733463	19850513
US 4880921	A	19891114	US 1987-75830	19870720
US 4900837	A	19900213	US 1987-76191	19870721
EP 334853	A1	19891004	EP 1987-907186	19871013
EP 334853	B1	19930609		

R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AT 90355	E	19930615	AT 1987-907186	19871013
US 4880816	A	19891114	US 1987-116583	19871104
US 5008257	A	19910416	US 1989-295938	19890111
US 5187158	A	19930216	US 1991-639283	19910110
US 5525727	A	19960611	US 1992-967979	19921028
PRIORITY APPLN. INFO.:			US 1982-379316	A2 19820518
			US 1983-461543	A2 19830127
			US 1983-475493	A2 19830315
			CA 1983-428192	A 19830516
			US 1983-516382	A2 19830722
			JP 1982-101940	A 19820614
			EP 1983-902034	P 19830512
			WO 1983-US725	A 19830512
			WO 1983-WO725	A 19830512
			ES 1983-522489	A 19830517
			IE 1983-1149	A 19830517
			ZA 1983-3521	A 19830517
			IT 1983-48327	A 19830518
			US 1984-665940	A2 19841029
			US 1985-733463	A3 19850513
			EP 1987-907186	A 19871013
			WO 1987-US2590	A 19871013
			US 1989-295938	A3 19890111
			US 1991-639283	A3 19910110

OTHER SOURCE(S): CASREACT 112:7383; MARPAT 112:7383  
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III

AB Compds. of the formula  $D(DHC)_n$  (I) [ $D$  = residue of a centrally acting drug having anticonvulsant, sedative and/or hypnotic properties, said drug being a hydantoin or barbiturate or an analog of a hydantoin or barbiturate, said drug containing at least one reactive amide or imide functional group, said residue being characterized by the absence of a H atom from at least one of said amide or imide functional groups in said drug;  $n$  = pos. integer equal to the number of said functional groups from which a H atom is absent;  $DHC$  = reduced, biooxidizable, blood-brain barrier penetrating, lipoidal form of a dihydropyridine-pyridinium salt redox carrier;  $DHC = Q1, Q2$ , etc.;  $R = H$ , C1-7 alkyl, C3-8 cycloalkyl, C1-7 haloalkyl, etc.;  $R1 = C1-7$  alkyl, haloalkyl, C7-10 aralkyl; dotted line indicates the presence of a double bond in position 4 or 5 of the dihydropyridine ring or position 2 or 3 of the dihydroquinoline ring] were prepared as brain-specific prodrugs. Quaternary salts of the formula  $D(QC^+)nqX-t$  (II) ( $D$  = as given above;  $X^-$  = anion of a pharmaceutically acceptable organic or inorg. acid;  $t$  = valence of acid anion;  $q$  = number which when multiplied by  $t$  is equal to  $n$ ;  $QC^+$  = hydrophilic, ionic pyridinium salt form of a dihydropyridine-pyridinium salt redox carrier;  $QC^+ = Q3, Q4$ , etc.;  $R, R1$  = as given above;  $n$  = pos. integer equal to the number of said functional groups from which a H atom is absent) were prepared as intermediates for I. Reaction of 5,5-diphenyl-3-hydroxymethyl-2,4-imidazolidinedione with nicotinic anhydride, followed by methylation with MeI and reduction, gave 5,5-diphenyl-3-[(1'-methyl-1',4'-dihydropyridin-3'-yl)carbonyloxymethyl]-2,4-imidazolidinedione. After one single injection of 1-methyl-3-[[N-[ $\beta$ -(3,4-dipivaloxyphenyl)ethyl]]carbamoyl-1,4-dihydropyridine to a rat, the pyridinium compound III could be seen to appear and then to disappear quickly from the blood, with a half-life of 27 min. On the contrary, the concentration of III increases in the brain steadily, reaching a maximum at about 30 min following administration. For III, the half-life of disappearance from the brain is about 3.2 h.

L2 ANSWER 43 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1989:428472 HCAPLUS  
 DOCUMENT NUMBER: 111:28472

09872705

TITLE: The utilization of prodrugs to enhance transdermal absorption of **testosterone**, deoxycorticosterone and indomethacin  
AUTHOR(S): Milosovich, S. M.; Hussain, Anwar A.; Hussain, M.; Dittert, Lewis W.  
CORPORATE SOURCE: Coll. Pharm., Univ. Kentucky, Lexington, KY, 40536, USA  
SOURCE: Progress in Clinical and Biological Research (1989), 292(Biol. Synth. Membr.), 273-7  
CODEN: PCBRD2; ISSN: 0361-7742  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Ester prodrugs which contain a protonated tertiary amine at physiolo. pH were used successfully to enhance the skin penetration of indomethacin, deoxycorticosterone, and **testosterone**. The prodrugs are enzymically hydrolyzed to their active parent compds. in the body, and therefore are expected to elicit the desired pharmacol. response.

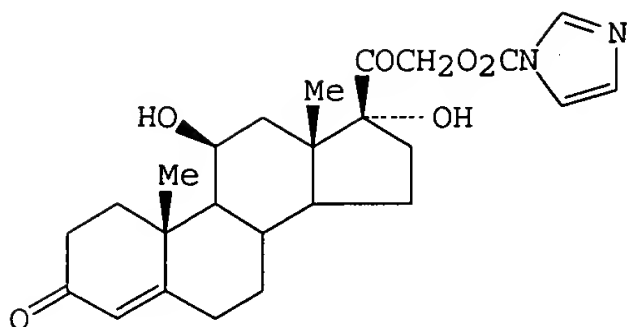
L2 ANSWER 44 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1989:428418 HCAPLUS  
DOCUMENT NUMBER: 111:28418  
TITLE: Studies on long-acting aryl carboxylic acid esters of **testosterone**  
AUTHOR(S): Leung, S. L.; Becket, G.; Karunanithy, R.; Low, K. F.; Fell, J. T.  
CORPORATE SOURCE: Dep. Pharm., Natl. Univ. Singapore, Singapore, 0511, Singapore  
SOURCE: Pharmaceutica Acta Helvetiae (1989), 64(4), 121-4  
CODEN: PAHEAA; ISSN: 0031-6865  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB A series of aryl carboxylic acid esters of **testosterone** were synthesized as possible agents for long-acting steroid therapy. The solubilities, partition coeffs., and hydrolysis rate consts. of the compds. were determined. The partition coeffs. increased with increasing chain length and they were in agreement with calculated values. The hydrolysis rates decreased with increasing chain length except for the first member of the series (benzoate ester) which exhibits the slowest rate, possibly due to the hydrolytic attack being hindered by steric and electronic effects.

L2 ANSWER 45 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1985:67298 HCAPLUS  
DOCUMENT NUMBER: 102:67298  
TITLE: Prodrugs as drug delivery systems. XXIX. Imidazole-1-carboxylic acid esters of hydrocortisone and **testosterone**  
AUTHOR(S): Klíxbull, Ulla; Bundgaard, Hans  
CORPORATE SOURCE: Dep. Pharm. Chem., R. Dan. Sch. Pharm., Copenhagen, DK-2100, Den.  
SOURCE: Archiv for Pharmaci og Chemi, Scientific Edition (1983), 11(4), 1065-74  
CODEN: AVPCCS; ISSN: 0302-248X  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB The kinetics of hydrolysis of hydrocortisone imidazole-1-carboxylic acid ester (I) [51988-89-7] and **testosterone** imidazole-1-carboxylic acid ester [51242-05-8] was studied to assess their suitability as **prodrug** forms. The pH-rate profiles of the 2 derivs. were derived in the range pH 1-12 and were accounted for by assuming spontaneous hydrolysis of the protonated forms (pKa 3.3-3.5) and OH--catalyzed hydrolysis of the free base forms. At pH 7.4 and 37° the half-life of hydrolysis of I was 8 min and that for the **testosterone** derivative 65 h. These rates were not significantly altered in the presence of human plasma. Due to protonation of the imidazole group, the derivs. showed increased solubility in acidic aqueous solution, the enhancement amounting to a factor of 16 for the **testosterone** derivative

L2 ANSWER 46 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
 ACCESSION NUMBER: 1982:91670 HCAPLUS  
 DOCUMENT NUMBER: 96:91670  
 TITLE: Prolonged action drug formulation  
 INVENTOR(S): Swarbrick, James  
 PATENT ASSIGNEE(S): University of California, Los Angeles, USA  
 SOURCE: PCT Int. Appl., 20 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8102975	A1	19811029	WO 1981-US520	19810420
W: AU, DK, JP				
RW: CH, DE, FR, GB, NL, SE				
AU 8172201	A1	19811110	AU 1981-72201	19810420
EP 50650	A1	19820505	EP 1981-901250	19810420
R: CH, DE, FR, GB, NL, SE				
CA 1168581	A1	19840605	CA 1981-375991	19810422
PRIORITY APPLN. INFO.:			US 1980-142279	A 19800421
			WO 1981-US520	A 19810420

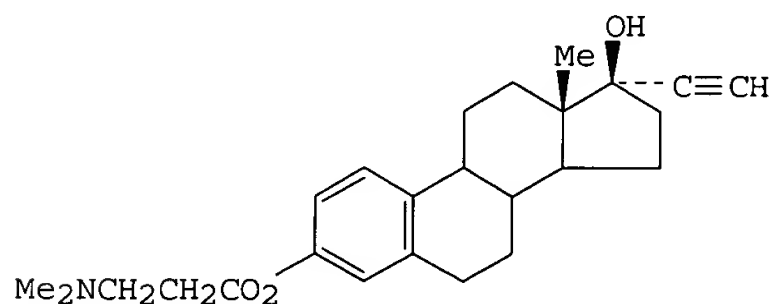
AB A prolonged-action drug formulation comprises a drug in solid form and a solid chemical derivative of the drug in a concentration sufficient to prolong the time during which the drug is active and having, at said concentration, minor pharmacol. activity relative to the drug. Thus, dapsone [80-08-0] and acedapsone [77-46-3] each at 0.5 g can be admixed, the mixture suspended in 3 mL H2O for injection and administered to a person suffering from leprosy as an i.m. injection of 3 mL (containing 1 g of the combination), the

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injection being repeated only once/mo instead of the typical dosage of 50-100 mg/day for 5 yr or more.

L2 ANSWER 47 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1982:69405 HCAPLUS  
DOCUMENT NUMBER: 96:69405  
TITLE: Synthesis of polymers with pharmacological properties.  
Introduction of peptide sequences into the  
macromolecular chain  
AUTHOR(S): Pleurdeau, A.; Rabadeux, J. C.; Gueniffey, H.; Lenuz, C.  
CORPORATE SOURCE: Fac. Sci., Univ. Maine, Le Mans, 72017, Fr.  
SOURCE: European Polymer Journal (1981), 17(9), 999-1003  
CODEN: EUPJAG; ISSN: 0014-3057  
DOCUMENT TYPE: Journal  
LANGUAGE: French  
AB Polypeptides were prepared from N-carboxyanhydrides bearing active steroidal groups. Introduction of peptide sequences into polymers with pharmacol. properties increased the biocompatibility of the macromol. **prodrug**. Lysine Cu complex reacted with the chloroformates of cholesterol and **testosterone** to give Cu complexes of H-Lys(CO<sub>2</sub>R)-OH (R = cholesteryl, testosteryl). The latter Cu complexes were deblocking and cyclized with COCl<sub>2</sub> to give the corresponding N-carboxyanhydrides. The polymerization of these carboxyanhydrides alone and with glycine N-carboxyanhydride gave oligopeptides bearing a steroidal backbone as a side group. The low mol. weight of the synthesized compds., the limited H<sub>2</sub>O solubility and the presence of secondary products limited the development of the method.

L2 ANSWER 48 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1978:500578 HCAPLUS  
DOCUMENT NUMBER: 89:100578  
TITLE: Steroid antifertility agents. Ionic complexes of basic derivatives for prolonged action  
AUTHOR(S): Gray, Allan P.; Yamauchi, Terry N.  
CORPORATE SOURCE: Chem. Chem. Eng. Res. Div., Res. Inst., Chicago, IL, USA  
SOURCE: Journal of Medicinal Chemistry (1978), 21(7), 712-15  
CODEN: JMCMAR; ISSN: 0022-2623  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB Ethynylestradiol 3-dimethylaminopropionate (I) [60257-22-9], sym-[66818-36-8] and anti-norethindrone 3-(O-dimethylaminopropyl)oxime [66818-34-6], and **testosterone** 3-(O-dimethylaminopropyl)oxime [66818-35-7] were prepared and converted to Zn and Al tannate complexes and

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were tested as potential long-acting **prodrug** forms of the parent steroids. The Zn tannate complex of I administered s.c. in an Al monostearate gel, had a prolonged duration of antifertility activity in rats. All of the basic derivs. and complexes had appropriate hormonal activities but in acute tests were less active than the resp. parents.

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FILE 'STNGUIDE' ENTERED AT 16:42:25 ON 26 APR 2005

FILE 'HCAPLUS' ENTERED AT 16:42:37 ON 26 APR 2005

L1 57193 S TESTOSTERONE  
L2 48 S L1 AND PRODRUG  
L3 6 S L2 AND ETHER  
L4 17 S L2 AND ESTER

=> d 12 21-34 ibib hitstr abs

L2 ANSWER 21 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:392436 HCAPLUS

DOCUMENT NUMBER: 135:204880

TITLE: A novel cytochrome P450 enzyme responsible for the metabolism of ebastine in monkey small intestine

AUTHOR(S): Hashizume, Takanori; Mise, Masashi; Matsumoto, Satoshi; Terauchi, Yoshiaki; Fujii, Toshihiko; Imaoka, Susumu; Funae, Yoshihiko; Kamataki, Tetsuya; Miyazaki, Hisashi

CORPORATE SOURCE: Developmental Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Osaka, 564-0053, Japan

SOURCE: Drug Metabolism and Disposition (2001), 29(6), 798-805  
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Small intestinal microsomes of cynomolgus monkeys were found to catalyze hydroxylation and dealkylation of an H1-antihistamine **prodrug**, ebastine. To identify the main enzyme responsible for ebastine hydroxylation, which has been hitherto unknown, we purified two cytochrome P 450 isoforms, named P 450 MI-2 and P 450 MI-3, from the intestinal microsomes on the basis of the hydroxylation activity. P 450 MI-2 and P 450 MI-3 showed the resp. apparent mol. wts. of 56,000 and 53,000 on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The internal amino acid sequence of P 450 MI-2 had high similarity with those of human CYP4F2, CYP4F3, and CYP4F8. The first 27 amino acid residues of P 450 MI-3 were highly homologous with those of monkey CYP3A8 and human CYP3A4/5/7. Furthermore, P 450 MI-2 and P 450 MI-3 were recognized by anti-CYP4F and anti-CYP3A antibodies, resp., in immunoblot anal. and catalyzed leukotriene B4  $\omega$ -hydroxylation and **testosterone** 6 $\beta$ -hydroxylation, which are known to be mediated by CYP4F and CYP3A, resp. Although both enzymes had ebastine hydroxylation activity, the Vmax value of P 450 MI-2 was much higher than that of P 450 MI-3 (37.0 vs. 0.406 nmol/min/nmol of P 450), and the former KM (5.1  $\mu$ M) was smaller than the latter KM (10  $\mu$ M). Anti-CYP4F antibody inhibited the hydroxylation in small intestinal microsomes strongly (70%), but anti-CYP3A antibody did not. These results indicate that P 450 MI-2



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belongs to the CYP4F subfamily and is mainly responsible for hydroxylation of ebastine in monkey small intestinal microsomes. This suggests that the small intestinal CYP4F enzyme, P 450 MI-2, can play an important role in the metabolism of drugs given orally.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 22 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2000:592532 HCAPLUS  
DOCUMENT NUMBER: 133:183007  
TITLE: Preparation of phosphocholine linked **prodrug** derivatives  
INVENTOR(S): Morimoto, Bruce H.; Barker, Peter L.  
PATENT ASSIGNEE(S): Amur Pharmaceuticals, Inc., USA  
SOURCE: PCT Int. Appl., 29 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048572	A1	20000824	WO 2000-US4140	20000216
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1161226	A1	20011212	EP 2000-908713	20000216
EP 1161226	B1	20040526		
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2002537243	T2	20021105	JP 2000-599364	20000216
AT 267586	E	20040615	AT 2000-908713	20000216
PRIORITY APPLN. INFO.:			US 1999-120483P	P 19990218
			WO 2000-US4140	W 20000216

OTHER SOURCE(S): MARPAT 133:183007

AB Prodrugs containing phosphocholines enhance the bioavailability of the linked drugs wherein the linker is (i) substituted or unsubstituted alkyl, (ii) substituted or unsubstituted alkenyl, (iii) substituted or unsubstituted alkanoyl, (iv) substituted or unsubstituted alkenoyl and wherein the therapeutic agent is an alc.-containing water-insol. steroid. A phosphocholine-linked propofol [{2',6'-diisopropylphenyl 4-(2-trimethylammoniummethoxy)phosphonobutyrate}] was prepared starting from trans-Et 4-hydroxycrotonate and through a sequence of reactions involving propofol and 2-chloro-2-oxo-1,3,2-dioxaphospholane. The **prodrug** was tested for its sedative activity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 23 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 2000:547377 HCAPLUS  
DOCUMENT NUMBER: 133:155440  
TITLE: In situ activation of microcapsules

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INVENTOR(S): Morrison, Dennis R.; Mosier, Benjamin  
PATENT ASSIGNEE(S): United States National Aeronautics and Space  
Administration, USA  
SOURCE: U.S., 28 pp., Cont.-in-part of U.S. 5,827,531.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 9  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6099864	A	20000808	US 1998-79741	19980515
US 349169	A0	19971007	US 1994-349169	19941202
US 5827531	A	19981027		
WO 9959554	A1	19991125	WO 1999-US10653	19990514

W: JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE

PRIORITY APPLN. INFO.: US 1994-349169 A2 19941202  
US 1998-79741 A 19980515

AB Disclosed are microcapsules comprising a polymer shell enclosing two or more immiscible liquid phases in which a drug, or a **prodrug** and a drug activator are partitioned into sep. phases, or prevented from diffusing out of the microcapsule by a liquid phase in which the drug is poorly soluble. Also disclosed are methods of using the microcapsules for in situ activation of drugs, where upon exposure to an appropriate energy source the internal phases mix and the drug is activated in situ. An example of a microcapsule, suitable for in situ activation of a **prodrug** is shown schematically. In this embodiment the **prodrug**, floxuridine, may be contained in the continuous, internal aqueous phase. The activator, thymidine kinase is also contained within the microcapsule. During irradiation with UV light of 300-390 nm, the internal liquid phases in the microcapsules exhibit a spontaneous, vigorous mixing action with brings the contents of the two phases together, and increases the activation kinetics of the water soluble floxuridine to the water insol. active form 5-FU, which diffuses out of the microcapsule.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 24 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1999:753042 HCAPLUS  
DOCUMENT NUMBER: 131:356128  
TITLE: In situ activation of microcapsules  
INVENTOR(S): Morrison, Dennis R.; Mosier, Benjamin  
PATENT ASSIGNEE(S): NASA/Johnson Space Center, USA  
SOURCE: PCT Int. Appl., 62 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 9  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959554	A1	19991125	WO 1999-US10653	19990514

W: JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE

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US 6099864 A 20000808 US 1998-79741 19980515  
PRIORITY APPLN. INFO.: US 1998-79741 A 19980515  
US 1994-349169 A2 19941202

AB Disclosed are microcapsules comprising a polymer shell enclosing two or more immiscible liquid phases in which a drug, or a **prodrug** and a drug activator are partitioned into sep. phases, or prevented from diffusing out of the microcapsule by a liquid phase in which the drug is poorly soluble. Also disclosed are methods of using the microcapsules for in situ activation of drugs, where upon exposure to an appropriate energy source the internal phases mix and the drug is activated in situ. The **prodrug**, floxuridine may be contained in a continuous, internal aqueous phase. The activator, thymidine kinase is also contained within the microcapsule. During irradiation with UV light of 300-390 nm, the internal liquid phases in the microcapsules had a spontaneous, vigorous mixing action which brings the contents of the 2 phases together, and increases the activation kinetics of the water soluble floxuridine to the water-insol. active form 5-FU, which diffuses out of the microcapsule.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 25 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:557633 HCAPLUS  
DOCUMENT NUMBER: 127:239118  
TITLE: Drug delivery systems containing ester sunscreens and penetration enhancers  
INVENTOR(S): Reed, Barry Leonard; Morgan, Timothy Matthias; Finnin, Barrie Charles  
PATENT ASSIGNEE(S): Monash University, Australia; Reed, Barry Leonard; Morgan, Timothy Matthias; Finnin, Barrie Charles  
SOURCE: PCT Int. Appl., 70 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 6  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729735	A1	19970821	WO 1997-AU91	19970219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2244089	AA	19970821	CA 1997-2244089	19970219
AU 9717134	A1	19970902	AU 1997-17134	19970219
AU 706967	B2	19990701		
EP 901368	A1	19990317	EP 1997-904304	19970219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000504697	T2	20000418	JP 1997-528834	19970219
US 6299900	B1	20011009	US 1998-125436	19981218
AU 9952589	A1	19991202	AU 1999-52589	19991001
US 2002028235	A1	20020307	US 2001-910780	20010724
US 6818226	B2	20041116		
US 2004013620	A1	20040122	US 2003-428016	20030502

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US 2004013621	A1	20040122	US 2003-428019	20030502
US 2004028625	A1	20040212	US 2003-428012	20030502
US 2004028725	A1	20040212	US 2003-428018	20030502
US 2004096405	A1	20040520	US 2003-636976	20030808
US 2004081684	A1	20040429	US 2003-644085	20030820
US 2004146469	A1	20040729	US 2004-759303	20040120

PRIORITY APPLN. INFO.:

AU 1996-8144	A	19960219
AU 1997-17134	A3	19970219
WO 1997-AU91	W	19970219
US 1998-125436	A3	19981218
US 2001-910780	A2	20010724

OTHER SOURCE(S): MARPAT 127:239118

AB A transdermal drug delivery system which comprises at least one physiol. active agent or **prodrug** thereof and at least one dermal penetration enhancer; characterized in that the dermal penetration enhancer is a safe skin-tolerant ester sunscreen. A non-occlusive, percutaneous or transdermal drug delivery system which comprises: (1) an effective amount of at least one physiol. active agent or **prodrug** thereof; (2) at least one non-volatile dermal penetration enhancer; and (3) at least one volatile liquid; characterized in that the dermal penetration enhancer is adapted to transport the physiol. active agent across a dermal surface or mucosal membrane of an animal, including a human, when the volatile liquid evaps., to form a reservoir or depot of a mixture comprising the penetration enhancer and the physiol. active agent or **prodrug** within said surface or membrane; and the dermal penetration enhancer is of low toxicity to, and is tolerated by, the dermal surface or mucosal membrane of the animal. The mean flux of 2% ketoprofen in 70% volume/volume aqueous ethanol through shed snakes kinetics in presence of 2% octyl salicylate in 70% volume/volume aqueous ethanol was 27.66 as compared to 2.58  $\mu\text{g}/\text{cm}^2\cdot\text{h}$  for azone. A transdermal aerosol contained 17 $\beta$ -estradiol 2, octyl dimethyl-p-aminobenzoate 8, ethanol 69, and di-Me ether 30%.

L2 ANSWER 26 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:335797 HCAPLUS

DOCUMENT NUMBER: 127:44396

TITLE: Enhanced cyclophosphamide and ifosfamide activation in primary human hepatocyte cultures: response to cytochrome P-450 inducers and autoinduction by oxazaphosphorines

AUTHOR(S): Chang, Thomas K. H.; Yu, Li; Maurel, Patrick; Waxman, David J.

CORPORATE SOURCE: Division Cell Molecular Biology, Department Biology, Boston University, Boston, MA, 02215, USA

SOURCE: Cancer Research (1997), 57(10), 1946-1954  
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The anticancer oxazaphosphorine prodrugs cyclophosphamide and ifosfamide are activated in human liver by a 4-hydroxylation reaction catalyzed by multiple cytochrome P 450 (CYP) enzymes. In the present study, we used a cultured human hepatocyte model to identify possible inducers of the CYP-catalyzed activation of these two anticancer prodrugs. Treatment of primary cultures of human hepatocytes with phenobarbital, dexamethasone, or rifampin elevated hepatocyte microsomal oxazaphosphorine 4-hydroxylation by up to 200-400% of control for both drug substrates. These inductions were associated with corresponding increases in

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immunoreactive CYP2B6, CYP2C8, CYP2C9, and CYP3A4, all previously shown to catalyze oxazaphosphorine activation. Rifampin (1  $\mu$ M, 96-h exposure) was a particularly potent inducer of ifosfamide and cyclophosphamide 4-hydroxylation, as well as of CYP3A protein levels and CYP3A-dependent **testosterone** 6 $\beta$ -hydroxylation. CYP3A4, CYP2C8, and CYP2C9 protein levels were also increased by exposure of the hepatocytes to cyclophosphamide or ifosfamide (50  $\mu$ M), which thereby enhanced their own rates of 4-hydroxylation in the cultured hepatocytes. IN one human hepatocyte culture that contained the polymorphically expressed CYP3A5 in addition to the more widely expressed CYP3A4, only CYP3A4 was induced by cyclophosphamide, ifosfamide, and rifampin. These studies: (a) demonstrate an underlying metabolic basis for the clin. important oxazaphosphorine autoinduction pharmacokinetics seen with these drugs in cancer patients; and (b) identify rifampin and other CYP inducers as potentially useful for increasing the rates of cyclophosphamide 4-hydroxylation and ifosfamide 4-hydroxylation in human liver in a manner that could favorably impact the clin. pharmacokinetics of these anticancer prodrugs.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 27 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:287176 HCAPLUS

DOCUMENT NUMBER: 126:347281

TITLE: **Testosterone** prodrugs for improved drug delivery

INVENTOR(S): Hale, Ron L.; Lu, Amy T.; Solas, Dennis W.; Cormier, Michel J. N.

PATENT ASSIGNEE(S): Affymax Technologies N.V., UK; Alza Corporation

SOURCE: U.S., 30 pp., Cont.-in-part of U.S. Ser. No. 898,219, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 5622944	A	19970422	US 1995-434892	19950504
US 5607691	A	19970304	US 1995-449188	19950524
PRIORITY APPLN. INFO.:			US 1992-898219	B2 19920612
			US 1993-9463	B2 19930127
			US 1993-77296	B2 19930614
			US 1993-164293	B1 19931209

OTHER SOURCE(S): MARPAT 126:347281

AB Compns. and methods are provided for enhanced transdermal electrotransport of 17-hydroxy sterol compds., including **testosterone**. The parent sterols are modified at the 17-hydroxy position by covalent attachment of a charged chemical modifier. The chemical modifier provides the parent sterol with enhanced transport properties and is hydrolyzed under physiol. conditions to release the active parent compound. The composition comprises a 17-hydroxy sterol/chemical modifier complex, more generally represented by the formula (sterol-O-)C(O)-R-N(R1)(R2)(R3)+. The portion of the complex derived from the chemical modifier is indicated by C(O)-R-N(R1)(R2)(R3)+, where N(R1)(R2)(R3)+ represents a quaternary ammonium group and R1, R2, and R3 are independently selected from the group consisting of lower alkyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroalkyl, and heteroarylalkyl; or R1 and R2 together with the nitrogen

to which they are attached form a substituted heterocycle and R3 is lower alkyl, and R is a linking moiety, linking the (sterol-O)-C(O)- to the nitrogen atom.

L2 ANSWER 28 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:281690 HCAPLUS

DOCUMENT NUMBER: 126:338338

TITLE: Inhibition by omeprazole of proguanil metabolism: mechanism of the interaction in vitro and prediction of in vivo results from the in vitro experiments

AUTHOR(S): Funck-Brentano, Christian; Becquemont, Laurent; Leneveu, Anne; Roux, Annie; Jaillon, Patrice; Beaune, Philippe

CORPORATE SOURCE: Clinical Pharmacology Unit, Saint-Antoine University Hospital-School of Medicine, Paris, Fr.

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 280(2), 730-738  
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Both the antimalarial **prodrug** proguanil and the gastric proton pump inhibitor omeprazole are substrates for cytochrome P 450 (CYP)2C19 and CYP3A. However, the relative contribution of each enzyme to proguanil bioactivation to cycloguanil and to the metabolism of omeprazole, as well as their potential to interact, remains to be examined. The bioactivation of proguanil to its active metabolite cycloguanil was studied in vitro in human liver microsomes and in vivo in 12 healthy subjects, in the absence and in the presence of omeprazole. The formation of cycloguanil from proguanil exhibited biphasic kinetic behavior in four of six human livers, indicating that at least two enzymes are responsible for this metabolic step. Cycloguanil formation activity did not correlate with immunoreactive CYP3A4 content or with CYP3A4 activity, as measured by **testosterone** 6 $\beta$ -hydroxylation, suggesting that CYP3A4 plays a limited role in cycloguanil formation. Furthermore, troleandomycin (10  $\mu$ M) inhibited only 10 to 17% of cycloguanil formation at proguanil concns. of 100 and 500  $\mu$ M. At a proguanil concentration of 20  $\mu$ M, omeprazole at 10  $\mu$ M inhibited cycloguanil formation in vitro by 47  $\pm$  59%. These in vitro results were consistent with the results of our in vivo study in healthy subjects, which showed a 32  $\pm$  11% decrease in proguanil apparent oral clearance and a 65  $\pm$  8% decrease in proguanil partial metabolic clearance to cycloguanil in the presence of omeprazole (both  $P < .001$ ). We conclude that in vitro studies of proguanil metabolism and interactions are predictive of in vivo situations, that CYP2C19 is the main enzyme responsible for proguanil bioactivation to cycloguanil and that omeprazole inhibits this biotransformation in vitro and in vivo by inhibiting this enzyme.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 29 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:310727 HCAPLUS

DOCUMENT NUMBER: 125:18815

TITLE: Metabolism of **testosterone** and its ester derivatives in organotypic coculture of human dermal fibroblasts with differentiated epidermis

AUTHOR(S): Tamura, Mihoko; Sueishi, Toshihiko; Sugibayashi, Kenji; Morimoto, Yasunori; Juni, Kazuhiko; Hasegawa, Tetsuya; Kawaguchi, Takeo

09872705

CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Josai University,  
1-1 Keyakidai, Sakado, Saitama, 35002, Japan  
SOURCE: International Journal of Pharmaceutics (1996), 131(2),  
263-271  
CODEN: IJPHDE; ISSN: 0378-5173  
PUBLISHER: Elsevier  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The metabolism of **testosterone** (TS) and its 17-O-acyl derivs. (acyl = acetyl, benzoyl and hemisuccinoyl) was studied using radioactive compds. in organotypic coculture of human dermal fibroblasts (living skin equivalent, LSE). When TS was applied to the epidermal-side of LSE in a small volume of acetone solution, both 5 $\alpha$ -reduced and 17-dehydrogenated metabolites were observed in the dermal-side culture solution, though the formation of the 5 $\alpha$ -reduced metabolites, dihydrotestosterone (DHT) and dihydroandrosterone (DHA), depended greatly on the culture conditions. The metabolic activity of LSE for **testosterone** was higher than that of excised hairless-rat skin. The metabolism of ester prodrugs of TS in LSE was dependent on their physicochem. properties and susceptibility to enzymic hydrolysis. Application of acetyl-TS and benzoyl-TS resulted in a high formation of the 17-dehydrogenated metabolite, androstenedione (ADO), though a very small amount of the **prodrug** was observed in the dermal side. Succinoyl-TS, a hydrophilic ester with very low susceptibility to hydrolysis, was quite resistant to both 5 $\alpha$ -reduction and 17-dehydrogenation, and more than 90% of the radioactivity appearing on the dermal side was from the **prodrug** itself and from TS. The hydrophilic and enzymically stable TS derivative may be a good candidate compound with which to administer TS transdermally.

L2 ANSWER 30 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN  
ACCESSION NUMBER: 1996:181570 HCAPLUS  
DOCUMENT NUMBER: 124:233011  
TITLE: Preparation of glycoside prodrugs with enhanced water solubility.  
INVENTOR(S): Klemke, R.-Erich; Koreeda, Masato; Houston, Todd A.;  
Shull, Brian K.; Tuinman, Roeland J.  
PATENT ASSIGNEE(S): Harrier, Inc., USA  
SOURCE: PCT Int. Appl., 51 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 4  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9532981	A1	19951207	WO 1995-US7027	19950601
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5693767	A	19971202	US 1994-251869	19940601
AU 9526617	A1	19951221	AU 1995-26617	19950601
PRIORITY APPLN. INFO.:			US 1994-251869	A 19940601
			US 1991-644002	A2 19910122
			US 1991-733915	B2 19910722
			US 1992-815691	B2 19920124

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Glycosides of aliphatic, alicyclic, aliphatic-aromatic, and aromatic aglycons having

primary, secondary, or tertiary OH, SH, or CO<sub>2</sub>H groups with 2,3-dideoxy- $\alpha$ -D-erythrohex-2-enopyranoside fragments Q1-Q6 (A = acyl; X = O, S, CO<sub>2</sub>), were prepared. Thus, a mixture of 4-acetamidophenol and hexaacetyl D-maltol was refluxed with iodine in THF for 12 h to give 30% of an  $\alpha,\beta$ -glycoside, which was stirred with Ba(OH)<sub>2</sub> in MeOH to give glycoside (I). I had 8 times the H<sub>2</sub>O solubility of tylenol itself in phosphate-buffered saline at pH 7.4.

L2 ANSWER 31 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:135052 HCAPLUS

DOCUMENT NUMBER: 124:249920

TITLE: Synthesis of novel androgen-linked phosphoramidate mustard prodrugs and growth-inhibitory activity in human breast cancer cells.

AUTHOR(S): Roth, T.; Tang, W.; Eisenbrand, G.

CORPORATE SOURCE: Dep. Chem., Univ. Kaiserslautern, Kaiserslautern, D-67663, Germany

SOURCE: Anti-Cancer Drug Design (1995), 10(8), 655-66

CODEN: ACDDEA; ISSN: 0266-9536

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two androgen-linked phosphoramidate mustard prodrugs were synthesized. The androgens **testosterone** and 19-nortestosterone were linked through the 17 $\beta$ -position via an acetal bond to aldophosphamide. Proton-catalyzed, as well as cytochrome P 450-mediated cleavage of the acetal bond resulted in the release of aldophosphamide which decays into the ultimate cytotoxic species, phosphoramidate mustard. In a competitive cellular binding assay, the new prodrugs displayed approx. 10-12% affinity to androgen binding proteins in breast cancer cells, relative to **testosterone** (100%). In the sex hormone receptor-neg. cell line MDA-MB231, the **testosterone** and 19-nortestosterone conjugates have been found to be as effective as 4-hydroperoxycyclophosphamide. Both compds. were more active than 4-hydroperoxycyclophosphamide in receptor-pos. cell lines. No significant differences in response were observed, however, between receptor-neg. and receptor-pos. cell lines.

L2 ANSWER 32 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:784119 HCAPLUS

DOCUMENT NUMBER: 123:161032

TITLE: **Prodrug** versus drug effects of 150  $\mu$ g desogestrel or 3-keto-desogestrel combination with 30  $\mu$ g ethinylestradiol on hormonal parameters: relevance of the peak serum level of 3-keto-desogestrel

AUTHOR(S): Kuhl, H.; Jing-Hoffmann, C.; Fitzner, M.

CORPORATE SOURCE: Dep. Obstetrics Gynecology, J. W. Goethe Univ., Frankfurt-am-Main, Germany



09872705

SOURCE: Hormone Research (1995), 44(3), 126-32  
CODEN: HRMRA3; ISSN: 0301-0163  
PUBLISHER: Karger  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The pharmacokinetics and pharmacodynamics of 150 µg desogestrel (DG) or 150 µg 3-keto-desogestrel (KDG) in combination with 30 µg ethinylestradiol (EE) were compared in a cross-over study. While the EE levels as well as the area under the curve (AUC) of KDG did not differ, significantly higher peak levels of KDG were observed after intake of the KDG-containing formulation. As compared to the control cycle, LH and FSH were not reduced on day 3 of the first treatment cycle (3/I), but markedly suppressed on day 21 of the third cycle (21/III), the effects being more pronounced with the DG-containing pill. The serum levels of **testosterone**, free **testosterone**, androstenedione, androstanediol glucuronide, and dehydroepiandrosterone sulfate (DHEA-S) were significantly reduced already on day 3/I, while sex hormone-binding globulin (SHBG) was unchanged and corticosteroid-binding globulin (CBG) was increased. Thereafter, both SHBG and CBG rose markedly. The progressive decrease in DHEA-S correlated best with free **testosterone** and androstanediol glucuronide. The results indicate that the peak level of KDG is more important for the biol. effectiveness than the AUC or KDG which appears to antagonize the suppressive action of EE on gonadotropin release. The rapid decrease in the androgen levels seems to be due to a direct inhibitory action of the pill on ovarian and adrenal steroid biosynthesis.

L2 ANSWER 33 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:342893 HCAPLUS  
DOCUMENT NUMBER: 122:142214  
TITLE: Transdermal delivery of **testosterone** using micellar **prodrug** approach  
AUTHOR(S): Thassu, Deepak; Singh, M.; Vyas, S. P.  
CORPORATE SOURCE: RANBAXY LABORATORIES LIMITED, New Delhi, 110020, India  
SOURCE: Proceedings of the International Symposium on Controlled Release of Bioactive Materials (1994), 21ST, 463-4  
CODEN: PCRMEY; ISSN: 1022-0178  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Amelioration of lipophilicity of **testosterone** by incorporating hydrophilic nontoxic bioacceptable chemical moieties and thus achieving optimum structural configuration to get enhanced transdermal permeation across the viable skin was investigated. The benefit of this micellar **prodrug** approach was the production of non-cytotoxic metabolites, protection of drug from cutaneous metabolism, and thus improved bioavailability and concomitant reduction in side effects.

L2 ANSWER 34 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:229213 HCAPLUS  
DOCUMENT NUMBER: 122:10363  
TITLE: Preparation of **prodrug** esters  
INVENTOR(S): Budt, Karl-Heinz; Peyman, Anuschirwan  
PATENT ASSIGNEE(S): Hoechst A.-G., Germany  
SOURCE: Ger. Offen., 29 pp.  
CODEN: GWXXBX  
DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 1

4/26/05

09872705

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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DE 4308095	A1	19940915	DE 1993-4308095	19930313
PRIORITY APPLN. INFO.:			DE 1993-4308095	19930313
OTHER SOURCE(S):	MARPAT 122:10363			
AB	W(R5)a [I; R5 = e.g., O2C(CR11R12)sX(CR15R16)lNR21[(CR15R16)mNR21]oR24; R11,R12,R15,R16 = H or alkyl; R21 = H, (cyclo)alkyl, alkoxycarbonyl; R24 = H, (cyclo)alkyl, alkenyl, aryl, etc.; W = mono-, di-, or tri-dehydroxylated drug residue; X = O, S, (alkyl)imino, etc.; a = 1-3; l = 2 or 3; o = 0-3; s = 1-5] were prepared Thus, <b>testosterone</b> was bromoacetylated and the product condensed with MeNHCH2CH2NMeCO2CMe3 (preparation given) to give, after deprotection, I (R5 = O2CCH2NMeCH2CH2NHMe, W = dehydroxylated <b>testosterone</b> residue, a= 1).			

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androgen and prodrugs

PAT. NO.	Title
1 6,884,795	<a href="#">T Pharmaceutical compositions and uses for androst-5-ene-3.beta., 17.beta.-diol</a>
2 6,881,728	<a href="#">T 14- .beta., 17- .alpha.-hydroxymethylandrostande derivatives as androgens</a>
3 6,878,806	<a href="#">T Human secreted protein HTEEB42</a>
4 6,875,886	<a href="#">T Modified PSMA ligands and uses related thereto</a>
5 6,875,767	<a href="#">T (5-cyano-2-thiazolyl)amino-4-pyridine tyrosine kinase inhibitors</a>
6 6,872,724	<a href="#">T Polymorphs with tyrosine kinase activity</a>
7 6,872,715	<a href="#">T Benzoquinone ansamycins</a>
8 6,864,275	<a href="#">T Compounds and methods for use thereof in the treatment of cancer</a>
9 6,858,627	<a href="#">T Glucocorticoid mimetics, methods of making them, pharmaceutical compositions, and uses thereof</a>
10 6,858,598	<a href="#">T Method of using a matrix metalloproteinase inhibitor and one or more antineoplastic agents as a combination therapy in the treatment of neoplasia</a>
11 6,855,836	<a href="#">T 17-Methylene steroids, process for their production and pharmaceutical compositions that contain these compounds</a>
12 6,852,719	<a href="#">T Glucocorticoid receptor modulators</a>
13 6,852,709	<a href="#">T Biologically useful polyphosphates</a>
14 6,849,649	<a href="#">T N-phenpropylcyclopentyl-substituted glutaramide derivatives as inhibitors of neutral endopeptidase</a>
15 6,846,839	<a href="#">T Methods for treating diseases and disorders related to unregulated angiogenesis and/or vasculogenesis</a>
16 6,846,823	<a href="#">T Method of treating lower urinary tract disorders</a>
17 6,846,809	<a href="#">T PEI: DNA vector formulations for in vitro and in vivo gene delivery</a>

- 18 [6,838,584](#) **T** [Estrogen receptor modulators](#)
  - 19 [6,835,392](#) **T** [Dual enhancer composition for topical and transdermal drug delivery](#)
  - 20 [6,833,373](#) **T** [Method of using an integrin antagonist and one or more antineoplastic agents as a combination therapy in the treatment of neoplasia](#)
  - 21 [6,833,372](#) **T** [Non-peptide GnRH agents, Pharmaceutical compositions, and methods for their use](#)
  - 22 [6,831,102](#) **T** [Phenyl naphthol ligands for thyroid hormone receptor](#)
  - 23 [6,824,993](#) **T** [Antibodies that bind human prostate specific G-protein receptor HPRAJ70](#)
  - 24 [6,824,780](#) **T** [Anti-tumor antibody compositions and methods of use](#)
  - 25 [6,818,226](#) **T** [Dermal penetration enhancers and drug delivery systems involving same](#)
  - 26 [6,812,344](#) **T** [1-\(4-Arylpiperazin-1-yl\)-.omega.-\[N-\(.alpha.,.omega.-dicarboximidoL\)\]-alkan es useful as uro-selective .alpha.1-adrenoceptor blockers](#)
  - 27 [6,809,193](#) **T** [Antisense oligonucleotide compositions and methods for the modulation of JNK proteins](#)
  - 28 [6,805,876](#) **T** [Phosphate based biodegradable polymers](#)
  - 29 [6,800,655](#) **T** [Analogs of indole-3-carbinol metabolites as chemotherapeutic and chemopreventive agents](#)
  - 30 [6,797,704](#) **T** [Systemic delivery of compounds through non-invasive bladder administration](#)
  - 31 [6,794,393](#) **T** [Tyrosine kinase inhibitors](#)
  - 32 [6,794,363](#) **T** [Isolated amyloid inhibitor protein \(AIP\) and compositions thereof](#)
  - 33 [6,784,170](#) **T** [Synthesis of anti-estrogenic and other therapeutic steroids from 21-hydroxy-19-norpregna-4-en-3-one](#)
  - 34 [6,784,167](#) **T** [17-beta-hydroxysteroid dehydrogenase-II inhibitors](#)
  - 35 [6,780,854](#) **T** [Orally active androgens](#)
  - 36 [6,770,466](#) **T** [Human protein tyrosine phosphatase polynucleotides, polypeptides, and antibodies](#)
  - 37 [6,759,431](#) **T** [Compositions and methods for treating or preventing diseases of body passageways](#)
  - 38 [6,756,397](#) **T** [Prodrugs of CC-1065 analogs](#)
  - 39 [6,753,164](#) **T** [Nucleic acids encoding human serpin polypeptide HMCIS41](#)
  - 40 [6,750,213](#) **T** [Estrogen receptor modulators](#)
  - 41 [6,750,019](#) **T** [Antisense modulation of insulin-like growth factor binding protein 5 expression](#)
  - 42 [6,747,048](#) **T** [Pyridine-based thyroid receptor ligands](#)
  - 43 [6,740,646](#) **T** [Bioavailable prodrugs of androgenic steroids and related method](#)
  - 44 [6,740,333](#) **T** [Suppository and composition comprising at least one polyethylene glycol](#)
  - 45 [6,734,211](#) **T** [Compositions and methods for promoting nerve regeneration](#)
  - 46 [6,734,185](#) **T** [Pyrrolo\[3,4-d\]pyrimidines as corticotropin releasing factor \(CRF\) antagonists](#)
  - 47 [6,723,730](#) **T** [Capsaicin receptor ligands](#)
  - 48 [6,720,344](#) **T** [Methods and compositions for stimulating osteoblast proliferation or treating malignant cell proliferation and methods for selecting osteoblast proliferation stimulants](#)
  - 49 [6,716,821](#) **T** [Cytotoxic agents bearing a reactive polyethylene glycol moiety, cytotoxic conjugates comprising polyethylene glycol linking groups, and methods of making and using the same](#)
  - 50 [6,713,487](#) **T** [Compounds useful as modulators of melanocortin receptors and pharmaceutical compositions comprising same](#)
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**((testosterone AND prodrugs) AND ether): 426 patents.**  
**Hits 1 through 50 out of 426**

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testosterone and prodrugs and ether

PAT. NO.	Title
1 6,884,795	<a href="#">T Pharmaceutical compositions and uses for androst-5-ene-3.beta., 17.beta.-diol</a>
2 6,884,787	<a href="#">T Antisense modulation of transforming growth factor-beta 3 expression</a>
3 6,881,728	<a href="#">T 14-.beta., 17-.alpha.-hydroxymethylandrostande derivatives as androgens</a>
4 6,878,806	<a href="#">T Human secreted protein HTEEB42</a>
5 6,878,805	<a href="#">T Peptide-conjugated oligomeric compounds</a>
6 6,878,709	<a href="#">T 3,4-di-substituted pyridazinediones as CXC chemokine receptor antagonists</a>
7 6,878,697	<a href="#">T Phenylamino-pyrimidines and uses thereof</a>
8 6,875,886	<a href="#">T Modified PSMA ligands and uses related thereto</a>
9 6,870,046	<a href="#">T Antisense modulation of interferon gamma receptor 2 expression</a>
10 6,869,952	<a href="#">T Pyrrolo[2,1-f][1,2,4]triazine inhibitors of kinases</a>
11 6,867,039	<a href="#">T Antisense modulation of dual specific phosphatase 5 expression</a>
12 6,864,275	<a href="#">T Compounds and methods for use thereof in the treatment of cancer</a>
13 6,861,418	<a href="#">T 4-aryl substituted indolinones</a>
14 6,858,627	<a href="#">T Glucocorticoid mimetics, methods of making them, pharmaceutical compositions, and uses thereof</a>
15 6,855,730	<a href="#">T 3-methylidenyl-2-indolinone modulators of protein kinase</a>
16 6,855,700	<a href="#">T Antisense modulation of damage-specific DNA binding protein 1, p127 expression</a>
17 6,852,536	<a href="#">T Antisense modulation of CD36L 1 expression</a>
18 6,849,649	<a href="#">T N-phenpropylcyclopentyl-substituted glutaramide derivatives as inhibitors of neutral endopeptidase</a>
19 6,846,925	<a href="#">T Colchinol derivatives as angiogenesis inhibitors</a>

- 20 [6,846,809](#) **T** [PEI: DNA vector formulations for in vitro and in vivo gene delivery](#)
- 21 [6,844,010](#) **T** [Therapeutic treatment and prevention of infections with a bioactive materials encapsulated within a biodegradable-biocompatible polymeric matrix](#)
- 22 [6,838,283](#) **T** [Antisense modulation of survivin expression](#)
- 23 [6,835,392](#) **T** [Dual enhancer composition for topical and transdermal drug delivery](#)
- 24 [6,833,372](#) **T** [Non-peptide GnRH agents, Pharmaceutical compositions, and methods for their use](#)
- 25 [6,828,151](#) **T** [Antisense modulation of hematopoietic cell protein tyrosine kinase expression](#)
- 26 [6,828,149](#) **T** [Antisense modulation of PPP3R1 expression](#)
- 27 [6,825,337](#) **T** [Antisense modulation of PLML expression](#)
- 28 [6,825,201](#) **T** [Indole, azaindole and related heterocyclic amidopiperazine derivatives](#)
- 29 [6,825,198](#) **T** [5-HT receptor ligands and uses thereof](#)
- 30 [6,821,978](#) **T** [Xanthine phosphodiesterase V inhibitors](#)
- 31 [6,818,668](#) **T** [5-alkyl-7-alkylcarbonate-isoflavone ester and related method](#)
- 32 [6,818,226](#) **T** [Dermal penetration enhancers and drug delivery systems involving same](#)
- 33 [6,818,213](#) **T** [Cancer treatment compositions comprising therapeutic conjugates that bind to aminophospholipids](#)
- 34 [6,809,193](#) **T** [Antisense oligonucleotide compositions and methods for the modulation of JNK proteins](#)
- 35 [6,800,751](#) **T** [Reagent and process for protecting nucleoside hydroxyl groups](#)
- 36 [6,797,819](#) **T** [Alkaloids](#)
- 37 [6,797,725](#) **T** [Prodrugs of a 3-\(pyrrol-2-ylmethylidene\)-2-indolinone derivatives](#)
- 38 [6,794,406](#) **T** [Indole derivatives](#)
- 39 [6,794,363](#) **T** [Isolated amyloid inhibitor protein \(AIP\) and compositions thereof](#)
- 40 [6,793,938](#) **T** [Biodegradable compositions for the controlled release of encapsulated substances](#)
- 41 [6,784,170](#) **T** [Synthesis of anti-estrogenic and other therapeutic steroids from 21-hydroxy-19-norpregna-4-en-3-one](#)
- 42 [6,784,167](#) **T** [17-beta-hydroxysteroid dehydrogenase-II inhibitors](#)
- 43 [6,783,760](#) **T** [Combined cancer treatment methods using therapeutic conjugates that bind to aminophospholipids](#)
- 44 [6,780,854](#) **T** [Orally active androgens](#)
- 45 [6,780,853](#) **T** [Neuroactive steroids of the androstane and pregnane series](#)
- 46 [6,777,417](#) **T** [3-\(4,5,6,7-tetrahydroindol-2-ylmethylidene\)-2-indolinone derivatives as kinase inhibitors](#)
- 47 [6,770,466](#) **T** [Human protein tyrosine phosphatase polynucleotides, polypeptides, and antibodies](#)
- 48 [6,767,739](#) **T** [Antisense modulation of microsomal triglyceride transfer protein expression](#)
- 49 [6,763,607](#) **T** [Method for making homogeneous spray-dried solid amorphous drug dispersions utilizing modified spray-drying apparatus](#)
- 50 [6,762,025](#) **T** [Single-molecule selection methods and compositions therefrom](#)
- 

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**Results of Search in 1976 to present db for:**

**(testosterone AND ((prodrug AND ether) AND androgen)):** 128 patents.

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PAT. NO.	Title
1 6,884,795	<a href="#">T Pharmaceutical compositions and uses for androst-5-ene-3.beta., 17.beta.-diol</a>
2 6,878,806	<a href="#">T Human secreted protein HTEEB42</a>
3 6,875,886	<a href="#">T Modified PSMA ligands and uses related thereto</a>
4 6,864,275	<a href="#">T Compounds and methods for use thereof in the treatment of cancer</a>
5 6,858,627	<a href="#">T Glucocorticoid mimetics, methods of making them, pharmaceutical compositions, and uses thereof</a>
6 6,858,621	<a href="#">T 2-(quinolonyl)-fused heterocycles as androgen receptor modulators</a>
7 6,849,649	<a href="#">T N-phenpropylcyclopentyl-substituted glutaramide derivatives as inhibitors of neutral endopeptidase</a>
8 6,846,809	<a href="#">T PEI: DNA vector formulations for in vitro and in vivo gene delivery</a>
9 6,835,392	<a href="#">T Dual enhancer composition for topical and transdermal drug delivery</a>
10 6,833,372	<a href="#">T Non-peptide GnRH agents, Pharmaceutical compositions, and methods for their use</a>
11 6,831,093	<a href="#">T Non-steroidal ligands for the glucocorticoid receptor, compositions and uses thereof</a>
12 6,818,226	<a href="#">T Dermal penetration enhancers and drug delivery systems involving same</a>
13 6,809,193	<a href="#">T Antisense oligonucleotide compositions and methods for the modulation of JNK proteins</a>
14 6,794,363	<a href="#">T Isolated amyloid inhibitor protein (APIP) and compositions thereof</a>
15 6,787,531	<a href="#">T Pharmaceutical composition for use as a contraceptive</a>
16 6,784,167	<a href="#">T 17-beta-hydroxysteroid dehydrogenase-II inhibitors</a>
17 6,770,466	<a href="#">T Human protein tyrosine phosphatase polynucleotides, polypeptides, and antibodies</a>
18 6,753,164	<a href="#">T Nucleic acids encoding human serpin polypeptide HMCIS41</a>



- 19 [6,750,019](#) **T** [Antisense modulation of insulin-like growth factor binding protein 5 expression](#)
  - 20 [6,747,048](#) **T** [Pyridine-based thyroid receptor ligands](#)
  - 21 [6,735,470](#) **T** [Electrokinetic delivery of medicaments](#)
  - 22 [6,713,487](#) **T** [Compounds useful as modulators of melanocortin receptors and pharmaceutical compositions comprising same](#)
  - 23 [6,710,086](#) **T** [Protected forms of pharmacologically active agents and uses therefor](#)
  - 24 [6,706,700](#) **T** [14.beta.,15.beta.-methylene-17.alpha.-hydroxymethyl-androgens](#)
  - 25 [6,696,484](#) **T** [Method and compositions for regulation of 5-alpha reductase activity](#)
  - 26 [6,670,386](#) **T** [Bicyclic modulators of androgen receptor function](#)
  - 27 [6,670,346](#) **T** [Medical uses of a selective estrogen receptor modulator in combination with sex steroid precursors](#)
  - 28 [6,660,760](#) **T** [Heterocyclic aromatic compounds useful as growth hormone secretagogues](#)
  - 29 [6,660,756](#) **T** [N-phenpropylcyclopentyl-substituted glutaramide derivatives as inhibitors of neutral endopeptidase](#)
  - 30 [6,649,587](#) **T** [Polyamine analog conjugates and quinone conjugates as therapies for cancers and prostate diseases](#)
  - 31 [6,632,834](#) **T** [Compositions and methods for treating conditions responsive to estrogen](#)
  - 32 [6,630,453](#) **T** [Androgen derivatives and uses thereof](#)
  - 33 [6,607,916](#) **T** [Antisense inhibition of Casein kinase 2-alpha expression](#)
  - 34 [6,605,441](#) **T** [Antibodies against fibroblast growth factor 11](#)
  - 35 [6,602,902](#) **T** [Dha-pharmaceutical agent conjugates to improve tissue selectivity](#)
  - 36 [6,593,112](#) **T** [Polynucleotides encoding fibroblast growth factor 15](#)
  - 37 [6,586,000](#) **T** [Hydroxide-releasing agents as skin permeation enhancers](#)
  - 38 [6,583,179](#) **T** [Substituted aminoalkylamide derivatives as antagonists of follicle stimulating hormone](#)
  - 39 [6,582,724](#) **T** [Dual enhancer composition for topical and transdermal drug delivery](#)
  - 40 [6,576,636](#) **T** [Method of treating a liver disorder with fatty acid-antiviral agent conjugates](#)
  - 41 [6,573,289](#) **T** [Naphthalene derivatives, their production and use](#)
  - 42 [6,562,370](#) **T** [Transdermal administration of steroid drugs using hydroxide-releasing agents as permeation enhancers](#)
  - 43 [6,525,203](#) **T** [Heterocyclic aromatic compounds useful as growth hormone secretagogues](#)
  - 44 [6,518,292](#) **T** [Heterocyclic aromatic compounds usefults as growth hormone secretagogues](#)
  - 45 [6,518,257](#) **T** [1-substituted phenyl-1-\(1h-imidazol-4-yl\) alcohols, process for producing the same and use thereof](#)
  - 46 [6,512,002](#) **T** [Methods of treatment for premature ejaculation in a male](#)
  - 47 [6,477,410](#) **T** [Electrokinetic delivery of medicaments](#)
  - 48 [6,465,445](#) **T** [Medical uses of a selective estrogen receptor modulator in combination with sex steroid precursors](#)
  - 49 [6,455,307](#) **T** [Antisense modulation of casein kinase 2-alpha prime expression](#)
  - 50 [6,440,738](#) **T** [Antisense modulation of casein kinase 2-beta expression](#)
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**Results of Search in 1976 to present db for:**

**testosterone:** 5425 patents.

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PAT. NO.	Title
1 6,885,895	<a href="#">T Methods and systems for electrical and/or drug stimulation as a therapy for erectile dysfunction</a>
2 6,884,842	<a href="#">T Molecular compounds having complementary surfaces to targets</a>
3 6,884,795	<a href="#">T Pharmaceutical compositions and uses for androst-5-ene-3.beta., 17.beta.-diol</a>
4 6,884,787	<a href="#">T Antisense modulation of transforming growth factor-beta 3 expression</a>
5 6,884,601	<a href="#">T Method to detect fertilization potential of sperm</a>
6 6,884,418	<a href="#">T Use of ligand-mimicking agents and anti-neoplastic drugs in cancer therapy</a>
7 6,882,940	<a href="#">T Methods and devices for prediction of hypoglycemic events</a>
8 6,881,789	<a href="#">T Polyubiquitin based hydrogel and uses thereof</a>
9 6,881,729	<a href="#">T Bile compound and method of controlling behavior of lampreys therewith</a>
10 6,881,728	<a href="#">T 14-.beta., 17-.alpha.-hydroxymethylandrostande derivatives as androgens</a>
11 6,881,548	<a href="#">T Methods and kits for diagnosing tumorigenicity and determining resistance to the antineoplastic effects of antiestrogen therapy</a>
12 6,881,423	<a href="#">T Powdery composition for nasal administration</a>
13 6,881,421	<a href="#">T Nanoparticles comprising at least one polymer and at least one compound able to complex one or more active ingredients</a>
14 6,878,806	<a href="#">T Human secreted protein HTEEB42</a>
15 6,878,805	<a href="#">T Peptide-conjugated oligomeric compounds</a>
16 6,878,731	<a href="#">T Imidazole alkaloids from <i>Lepidium meyenii</i> and methods of usage</a>
17 6,878,709	<a href="#">T 3,4-di-substituted pyridazinediones as CXC chemokine receptor antagonists</a>
18 6,878,697	<a href="#">T Phenylamino-pyrimidines and uses thereof</a>

- 19 [6,878,548](#) **T** [Composition for use in electroporation](#)
  - 20 [6,878,547](#) **T** [Antisense oligonucleotides against tenascin for treating vitiligo](#)
  - 21 [6,878,529](#) **T** [Compounds for the treatment of sexual dysfunction](#)
  - 22 [6,875,886](#) **T** [Modified PSMA ligands and uses related thereto](#)
  - 23 [6,875,854](#) **T** [Compositions and methods for the improved diagnosis and treatment of germ cell tumors](#)
  - 24 [6,875,843](#) **T** [Prevention of diabetes and prolongation of the honeymoon phase of diabetes by administration of GnRH antagonists](#)
  - 25 [6,875,619](#) **T** [Microfluidic devices comprising biochannels](#)
  - 26 [6,875,606](#) **T** [Human .alpha.-7 nicotinic receptor promoter](#)
  - 27 [6,875,597](#) **T** [Isolated human drug-metabolizing proteins, nucleic acid molecules encoding human drug-metabolizing proteins, and uses thereof](#)
  - 28 [6,875,438](#) **T** [Preparations for topical administration of substances having antiandrogenic activity](#)
  - 29 [6,875,180](#) **T** [Electromagnetic interference immune tissue invasive system](#)
  - 30 [6,872,811](#) **T** [HRPCa9 and HRPCa10 nucleic acids and polypeptides](#)
  - 31 [6,872,569](#) **T** [In vitro production of haploid germ cells](#)
  - 32 [6,872,546](#) **T** [Hyaluronan-binding proteins and encoding genes](#)
  - 33 [6,872,406](#) **T** [Fusogenic properties of saposin C and related proteins and polypeptides for application to transmembrane drug delivery systems](#)
  - 34 [6,870,046](#) **T** [Antisense modulation of interferon gamma receptor 2 expression](#)
  - 35 [6,869,973](#) **T** [Nitrosated and nitrosylated taxanes, compositions and methods of use](#)
  - 36 [6,869,952](#) **T** [Pyrrolo\[2,1-f\]\[1,2,4\]triazine inhibitors of kinases](#)
  - 37 [6,867,216](#) **T** [Inhibitors of hedgehog signal pathways, compositions and uses related thereto](#)
  - 38 [6,867,039](#) **T** [Antisense modulation of dual specific phosphatase 5 expression](#)
  - 39 [6,867,005](#) **T** [Method and apparatus for increasing the dynamic range and accuracy of binding assays](#)
  - 40 [6,864,275](#) **T** [Compounds and methods for use thereof in the treatment of cancer](#)
  - 41 [6,864,250](#) **T** [N-acylated lipophilic amino acid derivatives](#)
  - 42 [6,864,248](#) **T** [Androgenic steroid compounds and a method of making and using the same](#)
  - 43 [6,864,245](#) **T** [Biocompatible poly-.beta.-1.fwdarw.4-N-acetylglucosamine](#)
  - 44 [6,864,103](#) **T** [Phthalamide-lanthanide complexes for use as luminescent markers](#)
  - 45 [6,863,902](#) **T** [Immediate release eplerenone compositions](#)
  - 46 [6,862,890](#) **T** [Process for production of nanoparticles and microparticles by spray freezing into liquid](#)
  - 47 [6,862,479](#) **T** [Spinal cord stimulation as a therapy for sexual dysfunction](#)
  - 48 [6,861,557](#) **T** [Process for preparing rac-bicalutamide and its intermediates](#)
  - 49 [6,861,508](#) **T** [Transcriptional intermediary factor-2](#)
  - 50 [6,861,432](#) **T** [Piperazine derivatives that destabilize androgen receptors](#)
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